Guideline-Based Management in Gastroenterology

A. B. R. Thomson

www.giandhepatology.com

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"The Democratization of Knowledge"

FORWARD

Throughout the history of medicine, and likely even earlier, physicians made decisions as to how to manage their patients based on the best available information. For the younger physician, this information is based largely upon what they are taught. The older physicians reinforced this with the wisdom which comes from experience. In the past, there was only slow development of new knowledge, new understanding of causes and associations, new surgical procedures, new therapies. Now, the half-life of medical knowledge is estimated to be less than five years. Both the junior and senior physician is faced with this mountain of facts, findings and even some fiction. The once-taught knowledge will now not be sufficient even for a few years of competence. We must continue to reinvent ourselves.

Invented was a new term, “CME” continued medical education, or some form of this. The individual physician remained responsible for her/his own information-gathering. Organizations developed- oh how we human primates like to organize ourselves –developed to assist capturing all this data and translating it into usable, reliable and “proven” clinical knowledge.

Also invented was another concept, with its own terms, “levels of evidence”. The austute physician reports a finding to share with colleagues. That one or few patient numbers was expanded to a group. But if your group (read “experience”) differs from mine, then who is correct? Enter the need for statistics, sampling, generalizability, and of cause the placebo. Yet not enough for the placebo to be a matched dummy, it had to be blind, and randomized!

In search of the holy grail, the truth and the realization that there are many truths, based on sampling inclusion / exclusion criteria, age, gender, race and a host of unrecognized factors, even meta-analyses do not always agree. Pity the poor hardworking, compassionate and caring physician, who simply wishes to know. “what is best for the patient sitting in front of me? Medicine gains clinical knowledge from groups, and valiantly tries to apply this to “the one”. How do we travel from evidence, to recommendations, to action?

In our own search for excellence, we read, attend meetings, consult one another, and make use of that mystical beast, “the literature”. The challenge grows to the same level of difficulty as the starting point of trying to translate that mountain of data into useable knowledge. Generally speaking, textbooks offer the suggestions of management and therapeutic options as the writter’s learned opinion, their opinion at the time of writing the text. From writing to publishing and then to reading by the learner, there

is a considerable delay. On top of this we need to have considered “the literature”, systemic reviews, meta-analyses, the outcome of consensus meeting, and published guidelines. These guidelines may be out of date, or may be timely but apply to patients in one country or ethnic (read “genetically different”) group. We must therefore view these texts such as guidelines to be just that, guidelines. Remember the old saying: “Laws (read guidelines) are for the guidance of wise men (read “persons”), and the blind obedience of fools”. We we all so wise as to acknowledge the justice of this distinction.

This almost unsurmountable challenge of knowledge generation and wisdom application must now, in this enlightened era, be skillfully interdigitated with so many issues pertaining to the patient and to the physician. We in a multicultural country such as Canada are only too well aware of the importance of the respect for heterogeneity and inclusiveness, and of the importance of these psychosocial, ethnic, religious and other human differences based upon varying value systems. We are helped in creating the ideal well-rounded competent, caring and compassionate (the 3 C’s) physician by the Royal College (of Physicians and Surgeons of Canada) and its introduction of the CanMeds roles, which every physician must address beyond the sometimes narrow borders of even the “3 C’s” modern physician.

In this text are presented recommendations of the indications for the treatment of disorders in gastroenterology and hepatology, as derived from major guidelines. Subtle differences between topic guidelines are acknowledged, and where no recent guidelines are available, I draw on consensus statements, systemic reviews and meta-analyses. And sometimes even a little bit of common sense which is no longer so common. A number of the pharmaceutical agents which are mentioned may not yet be approved by national authorities or by third party payers. I also strongly recommend the guidelines of the WGO (World Gastroenterology Organization), which address the issue of suggestions in the face of economic disparity and social injustice, and the variability of persons everywhere.

One of the often forgotten aspects of the preparation of management guidelines – often forgotten at least by those who have worked so hard and cleverly to prepare the guidelines – even the best laid plans for the application of these learned guidelines are useless unless the guidelines are widely distributed and accepted by practicing and not just by “publishing” physicians.

One of the major drawbacks to the usual procedure of publishing guidelines is that the very process of publication may impair their wide distribution. In the process of researching this book, the publishers of Canadian, American, British and other European journals containing major guidelines in gastroenterology and hepatology were contacted to obtain permission to publish just the usually only one line statements of recommendation (e.g. “in the patient with new onset dyspepsia, who is over the age of 50, an EGD must be performed to investigate the cause and to exclude the possibility of esophageal or gastric cancer”). Over 95% of the journals required a significant payment for the right to publish each short statement. The authors of the guidelines cannot even give away their guidelines, because they have to sign over the copyright to the journal that usually does not even reimburse them for preparing the document. In fact, some journals go so far as to strongly discouraging even “paraphrasing the guideline statements.

This author recognizes that he is very privileged to be in an institution which provides access to a wide range of medical journals, so that access to these overshore published guidelines is easy. If the physician were a practitioner in the town of North, she / he might subscribe to and read perhaps two or three journals. If the author found her / his colleagues talking about how very useful and practitioner-friendly a particular journal was, they might afford themselves a subscription. But if this author were to practice in less fortunate areas of the world, I could not simply buy one more subscription. So, I would not have the benefit of guidelines, restricted as I would be by costs and controls.

This leaves a good product, a new guideline, sitting idle on the shelf, awaiting effective marketing. I have tried to paraphrase from multiple published guidelines, and included meta-analysis and systemic reviews to be able to make simple and clear suggestions of recommendations. Of course, what you choose to practise will depend both upon your perspective of the relevance of the literature to your patient, their needs and wishes and special circumstances, within the limiting factors of drug availability by approval, and often painful socioeconomic considerations.

This author works to provide current information (see what commercialization has done – I write “current information”, to avoid saying Current Contents ® or Up To Date®!!), against the background of best evidence for indications inclusive and exclusive of modern management. Through the World Gastroenterology Organization (WGO), the material is made freely available to anyone worldwide who has access to the internet and the www. In this way all physicians will be on a level playing field in

terms of what is on the patient's treatment menu of options, the knowledge of indications and available therapies. We physicians are all life-time learners, and may benefit from "free to download" gastroenterology and hepatology books. Other learners, be they medical students, residents or fellow, may also benefit with the alarming exponential rise of the cost of obtain a medical degree. There is becoming a return to the "classification" of physicians – only those from privileged and affluent "upper class" families will become the physicians in the future. This is not right; the search for all rounded physician must always be inclusive of trainees from all walks of life.

This book series represents small steps taken slowly on solid ground, to broaden the reach of medical knowledge. Each one of us has a part we can play to give back as thanks to those who helped us in our professional careers. Each one of us may help in this process of the democratization of knowledge, and of peace through medicine.

The Approach

D	Diagnosis	D	Drugs (now, and for follow up / maintenance)
E	Explain	E	Endoscopic options
C	Consent, informed	S	Surgical options
L	Lifestyle	S	Screening, surveillance, vaccinations (SSV)

The words "management" and "treatment" are often used interchangeably. On an examination, you don't know whether the examiner wishes you to discuss the overall aspects of the management of the patient with the pathological condition, or just the treatment of the condition without consideration of the broader needs of the patient. The suggestion is therefore that unless it is made clear by the question, that such a question be answered broadly by considering nine steps of patient care, called "DECAL DESS".

- Diagnosis – Confirm the diagnosis
- Explanation – Explain to patient in appropriate language and tone the nature of their illness, the treatment options, the risk and benefits, emphasizing what are their choices; explain implications of diagnosis for screening needs of the family.

- Consent
  - Establish a management plan with the patient's consent and "buy-in", as well as where possible or appropriate, their family support, complementary and alternative medicine together with informed consent
- Associations
  - Treat underlying causes or associations
- Life style considerations
  - Life style changes
    - Diet
    - Exercise
    - Weight
    - Smoking
    - Sleeping
    - Hobbies and fun interests
    - Psychological and religion needs
    - Social interactions
- Drugs
  - Drug
    - Route
    - Dose
    - Duration
    - Interval
    - Stop-rules
    - Serious / common AEs (adverse effects)
    - Costs
    - Drug interactions
    - Genetic testing
- Endoscopy
  - Endoscopy procedures
- Surgery
  - Surgical options
- SSV
  - Screening, surveillance, vaccinations
- Special consideration
  - Pregnancy
  - Breast feeding
  - Renal / hepatic dosing
  - Drug interactions

If for example you were asked to give the treatment of GERD symptoms in a 55 year old man, yes you would confirm the symptoms / signs that supported the clinical suspicion of the diagnosis. But was there any testing to

determine if the symptoms are actually linked to reflux, is there reflux, is there reflux damage, is there an alternate diagnosis such as ischemic heart disease or non-cardiac chest pain. Has there been a clear management plan agreed to be the patient, has he been compliant with the many and important lifestyle issue. Don't just give the name of the general class of drugs (e.g. PPIs), but state "I would recommend to this patient that he take a PPI such as pantoprazole 40 mg once a day, half an hour before breakfast, for two weeks". What is the "stop rule"? You would recommend that the patient contact you in two weeks to report their progress, and together you would review the treatment plan – continue, increase to bid therapy, perform endoscopy. The patient is over 50 years of age; did you discuss the benefit of screening colonoscopy, even in an average risk person. Does he need EGD because he is middle-aged Caucasian male with a 10 year history of moderately severe reflux symptoms occurring 3 times a week?

Even you are asked the management of some GI or Hepatology condition you have never heard of (e.g. malakoplakia or non-specific colonic ulcers), you will likely receives passing marks for mentioning all the non-drug considerations.

- Economic Issues

In many countries such as Canada, Europe, Australia and New Zealand, heath care costs are spread over the entire population. This leaves the sick person to deal with their illness, and not with their banker – "for the better good of all".

When faced with economic issues and health care, please refer to the excellent guidelines developed by WGO, World Gastroenterology Organization (www.worldgastroenterology.org/).

- No cost resources

No cost resource through **www.giandhepatology.com**

For no cost ("Democratization of Medicine") program of current treatment options, please go to the WGO website click "abrt@giandhepatology.com, and select desired reading material in the areas listed below.

For those who wish a less-than-cost paper book version, please go to www.amazon.com, and enter the ISBN number.

GASTROENTEROLOGY

First Principle of Gastroenterology and Hepatology (ISBN; 978-1461038467)

A concise introduction and update of common disorders, the diagnostic approach and management.

Recommended for the Senior Medical Student, Resident in General Internal Medicine, as well as for the practising clinician who wishes a refresher.

GI Practice Review (ISBN: 978-1475219951)

A detailed and in-depth consideration of common and less common disorders, with background material, OSCE and Board-focused questions, and extensive answers. To challenge the reader, there are also teasers on trivia, “So You Want to be a Gastroenterologist!”

Recommended for the advanced GI Trainees, Academic Clinicians and Seasoned Practitioners who wish to refresh and upgrade their excellence.

Endoscopy and Diagnostic Imaging 2 parts (Part I [ISBN: 9781477400579]; Part II [ISBN: 9781477400654])

We choose to be Clinicians, Gastroenterologists, and Hepatologists. We depend on diagnostic imaging consultants for their expertise. Yet we need to refresh or knowledge behind our endoscopic skills, and review what we are looking for when we “review the films” with radiologists. Know the language, know what to look for, and know you can’t be fooled.

Scientific Basis for Clinical Practice in Gastroenterology and Hepatology (ISBN: 978-1475226645)

A short and snappy illustrated approach helping the clinician understand and appreciate the scientific basis to their clinical practice.

Recommended for all of us want as painless away as possible to learn and to relearn how things work in the GI tract and liver, and why we do some of the things we do.

Guideline-Based Management in Hepatology (ISBN-13:978-1502928078)

In this text are presented recommendations of the indications for the treatment of disorders in hepatology, as derived from major guidelines.

GENERAL INTERNAL MEDICINE

Achieving Excellence in the OSCE - Part I [ISBN: 978-1475283037, 410 pages]; Part II [ISBN: 978-1475276978, 466 pages]

Mastering The Boards and Clinical Examinations in Internal Medicine – Part I [ISBN: 978-1461024842, 816 pages }Part II [ISBN: 978-1478392736, 788 pages]

The gastroenterologist and hepatologist practices against the background of General Internal medicine. For the Advance Trainee preparing for their OSCE or Board Exam, this book will help you enormously preparing for scenarios based around taking a Directed History and Perform a Focused Examination.

Recommended for the Internist in all of us who needs to keep up and brush up on more than Gastroenterology and Hepatology.

Bits and Bytes (ISBN: 978-1478295365)

When on Clinical Rounds, have you ever noticed how the really sharp residents seem like clever "namedroppers", knowing just the right question at the right time" You can easily learn to do this too- when seeing / discussing the GIM / GI patient with "Such-and-Such" or "Something-or-Other", a quick glance at sample bedside questions will attract the staff attention to rocket you forwards to the best program in your area of interest.

- Guidelines

Publication of guidelines from learned professional organizations (e.g. AGA, ACE, BSG, AASLD, CAG, etc.) help to sift through an extensive medical literature which is not always available to all of us, review the evidence, and making suggestions or recommendations of what we should do in our practise, as well as how and when. Sometimes the levels of evidence will be excellent, sometime recommendations are based only on the agreement of so-called experts, sometimes we have only a meta-analysis or a single publication to rely upon. Occasionally, even the evidence-based medicine approach may be challenged.

In this publication of "Guideline-Based Management", the most recent guidelines in the English language are presented in their summary points (full details are available in the often extensive and well-referenced primary sources). Where management guidelines are available, these are provided, where appropriate and possible, considering the Nine Steps of Patient Care, "DECAL DESS", an acronym for Diagnosis, Explanation, Consent,

Association, Lifestyle Considerations, as well as Drugs, Endoscopy, Surgery, and SSV (screening, surveillance, vaccination).

The author has no conflict of any nature with any commercial, political or professional organization, and cannot / will not profit from any aspect of suggestions made from summarizing and where necessary editoralizing on the recommendations.

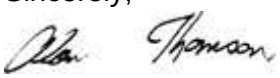
The trainee needs to be alert to what does the Seasonal and Respected Clinician say and do. When asked, for example, the causes of duodenal ulceration, she / he does not recite a catelog of possible and "you'll never see in your lifetime" diagnosis, but will provide a balanced list, balanced by what is Common and what is serous if missed.

The privileged physician who is in training in a very rich program or the clinician who does 40 endoscopic procedures per week with collectable billings of $200 each, may well be able to refer to and subscribe to the outstanding web-based Up-to-Date®. For the 90% of physician world-wide who are not so fortunate hopefully they we will find that this non-charge WGO-endorsed web-based and regularly updated source is refreshing, nicely detailed, and to-the-point.

This series of quality and up-to-date medical publication is provided by WGO through CAPstone publications to physicians and to physician trainees worldwide, with the intent that these be no discrimination of the cognitive component of the quality of healthcare around the world Gastrointestinal and Hepaticopancreaticobiliary Disorders.

Left to the politician, the tax payers, the NGOs, and the global perspective of benevolent agencies in time there will be the removal of the financial barriers of quality medical care to all. But we as proud and dedicated physicians have and will use our power of commitment to remove financial considerations as a gatekeeper to the knowledge of our fellow physicians worldwide, as we master our professional knowledge, while awaiting the opening of resources so that we may help to benefit "All God's Creatures", our Sisters and Brothers.

Sincerely,



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DISCLAIMER

The primary purpose of this publication is education. The author, editor and publisher acknowledge that the development of new material opens to way for possible errors – what is correct today might not be the standard of care tomorrow. Readers are advised to ensure that the doses of drugs which they use are in compliance with their country's product information, and that the use of any therapeutic agent, be it a pharmaceutical or a technology, should be directed by local guidelines. There is often a wide diversity of professional opinion, and guidelines from one country are not always congruent with another.

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INTRODUCTION AND GENERAL PRINCIPLES

The “Grade” of evidence relates to the strength of the recommendation. A strong recommendation suggests the recommendation should or should not be followed, whereas the clinical recommendation is one of “probably” – probably follow or do not follow the recommendation.

The evidence level relates to the quantity of the data which is available, upon which to make a consensus statement or to formulate a guideline. For example, consider the extremes of the reliability of two double-blind placebo-controlled randomized clinical trials with the appropriate power, versus the opinion expressed by a so-called expert, who is usually a middle-aged male physician in the “Ivory Tower” of an acclaimed institution, who spends most of his time teaching, doing research and traveling the words rather than engaging in a very busy clinical practice.

A further consideration is taken by the members of the guideline committee of the World Gastroenterology Organization, the WGO. The WGO guidelines also recognize the importance of the resources available to the patient and to their community health care facilities. For example, there may be Level I, grade A evidence to treat the constipated patient with lubiprostone, prucalopride or biofeedback, put even in a so-called “developed” and “have” (as compared to a “have not”) country, these pharmaceuticals may not be provided by a third-party coverage, and sophisticated testing, sacral nerve stimulation or biofeedback might only be provided hundreds of kilometers or miles away, and therefore rendering them in reality, unavailable, and as well awarding a worldwide common complaint of dyspepsia diarrhea or constipation with the subtext notation of “DOR”, a disease of the rich.

Thus, the physician and the patient need to consider treatment decisions in three dimensions: strength of the data, strength of the recommendation, and strength of the patients’ resources. This book will not release the limitation of the resources, but the no-cost internet access will remove the constraint of knowledge. And with knowledge, comes justice, social justice and equality of opportunity.

DEDICATION

To my special teachers

Robi Dunlop

Leslie Valberg

Sidney Truelove

Ivan Beck

John Dietschy

TABLE OF CONTENTS

GENERAL BACKGROUND

FDA PREGNANCY CATEGORY FOR DRUGS

- Give the **FDA Pregnancy Category "Xs**" for 8 drugs used in GI / Hepatology, as well as those which must be used with great caution.

Site	Clinical condition	"X Drugs"
➢ Esophagus	○ Candida	– Fluconazole ("azoles")
➢ Stomach	○ Dyspepsia	– Misoprostol
➢ Small bowel / Colon	○ Diarrhea	– Diphenoxylate with atropine
	○ Constipation	– Anthraquinones
		– 5-HT4 agonists
		– Prostaglandins (misoprostol)
	○ IBD	– Thalidomide
		– Corticosteroids - avoid in first trimester of pregnancy if possible
		– Cyclosporin – do not use during breast feeding
		– Methotrexate
		Avoid use of biologics during 3rd trimester
		– Adalimumab – data is not available on safety during breastfeeding
		– Certolizumab does not cross placenta and is a better choice than infliximab and adalimumab in 3rd trimester of pregnancy
➢ Liver	○ HCV	– Ribavirin
	○ Hemosiderosis	– Deferoxamine
	○ Wilson disease	– Penicillamine
	○ Transplantation	– MMF (mycophenolate mofetil)

Abbreviations: IBD, inflammatory bowel disease

- Give the **teratogenic effects** of 5 drugs or chemicals which should not be used in pregnancy.

For Certain

- Alcohol (ethanol) fetal alcohol syndrome (FAS)
  - Chronic daily intake
    - Maternal intake of 8 drinks per day (~ 2 g ethanol / kg per day) → 1/3 of offspring have full expression of syndrome
    - No safe lower limit
  - Features of FAS
    - ↓ growth
    - ↓ development
    - Dysmorphic face
    - Cleft palate
    - Cardiac defects
- Methotrexate
  - Maternal dose of > 10 mg / week
  - Defects
    - Intrauterine growth retardation
    - Mental retardation
    - Craniofacial abnormalities
    - Abnormal cranial ossification
    - Abnormal derivatives of first branchial arch
- Misoprostol
  - Defects in cranial nerves
    - VI
      - ↓ abduction of eye
    - VII
      - Facial palsy
  - Defects of limbs
  - Contraction of uterus (premature labour, abortion)

- Thalidomide
  - Single dose of < 1 mg / Kg at critical period of 34th to 50th day after the beginning of the last menses causes abnormalities in 1/5 of exposed children.
  - Abnormalities
    - Short limbs
    - Heart
    - Gut muscle
    - Ears

POSSIBLE TERATOGENIC DRUGS

- Fluconazole
  - Dysmorphic face
  - Congenital heart defects
  - Skeletal abnormalities
- Mycophenolate mofetil
  - Multiple synostosis
  - Disorders
    - CNS
    - Eye
    - Ear
    - Face
    - Palate
    - Heart
    - GI tract
    - GU tract
    - Skeletal, including fingers
- Penicillamine
  - Connective tissue disorders

Please see: www.motherisk.org/women/index.jsp

Check Up-To-Date safety of all drugs before prescribing in pregnancy and lactation.

Useful background: **Drugs and Breastfeeding**

<u>Drugs which are safe to use during breastfeeding</u>

DO NOT DRINK ALCOHOL. Stop smoking, and consume only moderate amounts of caffeine.

- Analgesics
  - Acetaminophen
  - Morphine
- Antibiotics
  - Aminoglycosides (when given po)
  - Cephalosporins
  - Macrolides
  - Metronidazole
  - Nitrofurantoin
  - Penicillins
  - Sulphonamides
    - Aide de Memoire
      "SPANC-M"
      S Sulphonamides
      P penicillins
      A Aminoglycosides
      N Nitrofurantoin
      C Clindamycin
      M Macrolides, metronidazole
- GI drugs
  - Dyspepsia
    - Antacids
    - Sucralfate
    - H2-receptor antagonists
    - Proton pump inhibitor
  - Prokinetics
    - Domperidone
    - Metoclopramide
  - Anti-diarrheals
    - Loperamide

- Laxatives
  - Bisacodyl
  - Docusate
  - Magnesium hydroxide
  - Psyllium
- Glucocorticosteroids
- NSADs
  - Ibuprofen
  - Diclofenac
  - Indomethacin
  - Naproxen (long half-life)

- Antifungals
  - Amphotericin B
  - Fluconazole
  - Ketoconazole
- Antivirals
  - Acyclovir

Adapted from: Ito S and Brochet MS. Appendix II. In: Therapeutic Choices. Grey J, Ed. 6th Edition, Canadian Pharmacists Association: Ottawa, ON, 2011, page 1730-1746.

DRUG DOSE ADJUSTMENTS IN RENAL DISEASE

- Drugs that are eliminated < 50% by the kidney may need empiric dose-adjustment for liver disease.
- Drugs that are > 50% eliminated by the kidney may need empiric adjustment for liver disease.
- The MDRD (Modification of Diet in Renal Disease) may be used to estimate GFR (glomerular filtration rate) to stage chronic renal disease, and the type of patient may benefit from consultation with a nephrologist.
- For the gastroenterologist, it may be adequate to estimate the GFR from the following equations to estimate ClCr (clearance of creatinine).

- Give 7 medications or classes of medications commonly used in gastroenterology / hepatology for which their doses need to be adjusted with impaired renal function (renal dosing).

- Esophagus / Stomach
  - Antacids containing magnesium
  - H2-receptor antagonist
  - Metoclopramide (dopamine antagonist)
  - ASA, NSAIDs, COXIBs
  - Acyclovir, fluconazole, cefotaxime, clarithromycin
- Small bowel
  - Azathioprine, 6-MP
  - Methotrexate
  - Cyclosporin
- Colon
  - Magnesium – phosphate containing osmotic laxatives
  - 5-HT3 antagonist, 5-HT4 agonist
  - C.difficile infection
  - Vancomycin
- Liver
  - Diuretics (furosemide, hydrochlorothiazide)
  - Fluoroquinolones
  - Sulfonamide combinations (sulfamethoxazole)
  - Pentoxifylline
  - Nucleos(t)ide analogues
  - HBV
    - Lamivudine
    - Adenofovir
    - Entecavir
    - Tenofovir

Useful background: GI Drugs and Renal Function

- Males

  $$\text{ClCr (mL / sec / 70 kg} = \frac{(140 - \text{age}) \times 1.5}{\text{Serum creatinine (µmol / L)}}$$

- Females
  - Multiply above by 0.85

- Dose-adjustment

May be achieved by reducing the dose or measuring the dosing intervals. Make use of trough measurement of drugs, where available.

			Normal dosing interval				
% renal excretion of drug	75% - 100%	50% - 74%	q4h	q6h	q8h	q12h	q24h
Estimated ClCr (mL / s / 70 Kg)	0.5 – 1.0	0.33 – 0.75	q6h	q8h	q12h	q24h	↓ by 25%
	0.25 – 0.5	0.16 – 0.33	q8h	q12h	q24h	q12h ↓ 25%	↓ by 50%
	< 0.25	< 0.16	q12h	q24h	q24h ↓ 25%	q24h ↓ 50%	q24h ↓ 75%

Abbreviation: ClCr, clearance of creatinine

Source: McCormack J et al. Appendix 1. In: *Therapeutic Choices*, Ottawa, Canada: Canadian Pharmacists Association 2011, page 1697-1719.

QUALITY PERFORMANCE INDICATORS

Esophagogastroduodenoscopy (EGD)

American Society for Gastrointestinal Endoscopy (ASGE)

American College of Gastroenterology (ACG) (Source: MK, et al., *Am J Gastroenterol* 2014;110:48-59.

- Indicators
  - Dyspepsia
    - Peptic ulcer disease suspected
      - Testing for Helicobacter pylori
  - Upper GI bleeding
    - Non variceal
      - Forrest classification of stigmata of bleeding risk (active bleeding [arterial or venous] invisible vessel)
      - Endoscopic hemostatic therapy
      - Proton pump inhibitor for suspected nonvarieal bleeding (i.e. peptic ulcer)
    - Variceal
      - Prophylactic antibiotics

- Indications and contraindications for EGD

1. EGD is generally indicated for evaluating:

A. Upper abdominal symptoms, which persist despite an appropriate trial of therapy

B. Upper abdominal symptoms associated with other symptoms or signs suggesting serious organic disease (e.g., anorexia and weight loss) or in patients aged >45 years

C. Dysphagia or odynophagia

D. Esophageal reflux symptoms, which are persistent or recurrent despite appropriate therapy

E. Persistent vomiting of unknown cause

F. Other diseases in which the presence of upper GI pathology might modify other planned management. Examples include patients who have a history of ulcer or GI bleeding who are scheduled for organ transplantation, long-term anticoagulation, or chronic nonsteroidal anti-inflammatory drug therapy for arthritis and those with cancer of the head and neck

G. Familial adenomatous polyposis syndromes

H. For confirmation and specific histologic diagnosis of radiologically demonstrated lesions:

1. Suspected neoplastic lesion

2. Gastric or esophageal ulcer

3. Upper tract stricture or obstruction

I. GI bleeding:

1. In patients with active or recent bleeding

2. For presumed chronic blood loss and for iron deficiency anemia when the clinical situation suggests an upper GI source or when colonoscopy result is negative

J. When sampling of tissue or fluid is indicated

K. In patients with suspected portal hypertension to document or treat esophageal varices

L. To assess acute injury after caustic ingestion

M. Treatment of bleeding lesions such as ulcers, tumors, vascular abnormalities (e.g., electrocoagulation, heater probe, laser photocoagulation, or injection therapy)

N. Banding or sclerotherapy of varices

O. Removal of foreign bodies

P. Removal of selected polypoid lesions

Q. Placement of feeding or drainage tubes (peroral, PEG, or percutaneous endoscopic jejunostomy)

R. Dilation of stenotic lesions (e.g., with transendoscopic balloon dilators or dilation systems by using guidewires)

S. Management of achalasia (e.g., botulinum toxin, balloon dilation)

T. Palliative treatment of stenosing neoplasms (e.g., laser, multipolar electrocoagulation, stent placement)

U. Endoscopic therapy for intestinal metaplasia

V. Intraoperative evaluation of anatomic reconstructions typical of modern foregut surgery (e.g., evaluation of anastomotic leak and patency, fundoplication formation, pouch configuration during bariatric surgery)

W. Management of operative adverse events (e.g., dilation of anastomotic strictures, stenting of anastomotic disruption, fistula, or leak in selected circumstances)

2. EGD is generally not indicated for evaluating:

A. Symptoms that are considered functional in origin (there are exceptions in which an endoscopic examination may be done once to rule out organic disease, especially if symptoms are unresponsive to therapy)

B. Metastatic adenocarcinoma of unknown primary site when the results will not alter management

C. Radiographic findings of:

1. Asymptomatic or uncomplicated sliding hiatal hernia

2. Uncomplicated duodenal ulcer that has responded to therapy

3. Deformed duodenal bulb when symptoms are absent or respond adequately to ulcer therapy

3. Sequential or periodic EGD may be indicated:

A. Surveillance for malignancy in patients with premalignant conditions (ie, Barrett's esophagus)

4. Sequential or periodic EGD is generally not indicated for:

A. Surveillance for malignancy in patients with gastric atrophy, pernicious anemia, or prior gastric operations for benign disease

B. Surveillance of healed benign disease such as esophagitis or gastric or duodenal ulcer

C. Surveillance during repeated dilations of benign strictures unless there is a change in status

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- Summary of proposed quality indicators for EGD

Quality indicator	Grade of recommendation	Type of measure	Performance target (%)
Preprocedure			
1. Frequency with which EGD is performed for an indication that is included in a published standard list of appropriate indications, and the indication is documented	1C+	Process	>80
2. Frequency with which informed consent is obtained, including specific discussions of risks associated with EGD, and fully documented	3	Process	>98
3. Frequency with which appropriate prophylactic antibiotics are given in patients with cirrhosis with acute upper GI bleeding before EGD (priority indicator)	1B	Process	>98
4. Frequency with which appropriate prophylactic antibiotics are given before placement of a PEG tube	1A	Process	>98
5. Frequency with which a PPI is used for suspected peptic ulcer bleeding (priority indicator)	1B	Process	>98
6. Frequency with which vasoactive drugs are initiated before EGD for suspected variceal bleeding	1B	Process	>98

Quality indicator	Grade of recommendation	Type of measure	Performance target (%)
Intraprocedure			
7. Frequency with which a complete examination of the esophagus, stomach, and duodenum, including retroflexion in the stomach, is conducted and documented	3	Process	>98
8. Among those with nonbleeding gastric ulcers, frequency with which gastric biopsies are done to exclude malignancy	2C	Process	>80
9. Frequency with which Barrett's esophagus is appropriately measured when present	2C	Process	>98
10. Frequency with which biopsies are obtained in cases of suspected Barrett's esophagus	2C	Process	>90
11. Frequency with which type of upper GI bleeding lesion is described, and the location is documented	3	Process	>80
12. Frequency with which, during EGD examination revealing peptic ulcers, at least one of the following stigmata is noted: active bleeding, nonbleeding visible vessels (pigmented protuberance), adherent clot, flat spot, and clean-based	1A	Process	>98

Quality indicator	Grade of recommendation	Type of measure	Performance target (%)
13. Frequency with which, unless contraindicated, endoscopic treatment is given to ulcers with active bleeding or with nonbleeding visible vessels (priority indicator)	1A	Process	>98
14. Frequency with which achievement of primary hemostasis in cases of attempted hemostasis of upper GI bleeding lesions is documented	3	Process	>98
15. Frequency with which a second treatment modality is used (e.g., coagulation or clipping) when epinephrine injection is used to treat actively bleeding or nonbleeding visible vessels in patients with bleeding peptic ulcers	1A	Process	>98
16. Frequency with which variceal ligation is used as the first modality of treatment for the endoscopic treatment of esophageal varices	1A	Process	>98
17. Frequency with which at least 4 intestinal biopsies are done from patients in whom celiac disease is suspected	1C	Process	>90

Quality indicator	Grade of recommendation	Type of measure	Performance target (%)
Postprocedure			
18. Frequency with which PPI therapy is recommended for patients who underwent dilation for peptic esophageal strictures	1A	Process	>98
19. Frequency with which patients diagnosed with gastric or duodenal ulcers are instructed to take PPI medication or an H2 antagonist	1A	Process	>98
20. Frequency with which plans to test for *H pylori* infection are documented for patients diagnosed with gastric or duodenal ulcers (priority indicator)	1A	Process	>98
21. Frequency with which patients with evidence of rebleeding from peptic ulcer disease after endoscopic treatment undergo repeat upper endoscopy	1B	Process	>98
22. Frequency with which patients are contacted to document the occurrence of adverse events after EGD	3	Process	N/A

[a] This list of potential quality indicators was meant to be a comprehensive listing of measurable endpoints. It is not the intention of the task force that all endpoints be measured in every practice setting. In most cases, validation may be required before a given endpoint may be universally adopted.

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Colonoscopy

- Appropriate Indications for Colonoscopy
  - Evaluation of an abnormality on barium enema or other imaging study that is likely to be clinically significant, such as a filling defect or stricture
  - Evaluation of unexplained GI bleeding
  - Hematochezia
  - Melena after an upper GI source has been excluded
  - Presence of fecal occult blood
  - Unexplained iron deficiency anemia
  - Screening and surveillance for colon neoplasia
  - Screening of asymptomatic, average-risk patients for colon neoplasia
  - Examination to evaluate the entire colon for synchronous cancer or neoplastic polyps in a patient with treatable cancer or neoplastic polyp
  - Colonoscopy to remove synchronous neoplastic lesions at or around the time of curative resection of cancer followed by colonoscopy at 1 year and, if examination normal, then 3 years, and, if normal, then 5 years thereafter to detect metachronous cancer
  - Surveillance of patients with neoplastic polyps
  - Surveillance of patients with a significant family history of colorectal neoplasia
  - For dysplasia and cancer surveillance in select patients with long-standing ulcerative or Crohn's colitis
  - For evaluation of patients with chronic inflammatory bowel disease of the colon, if more precise diagnosis or determination of the extent of activity of disease will influence management
  - Clinically significant diarrhea of unexplained origin
  - Intraoperative identification of a lesion not apparent at surgery (eg, polypectomy site, location of a bleeding site)
  - Treatment of bleeding from such lesions as vascular malformation, ulceration, neoplasia, and polypectomy site

- Intraoperative evaluation of anastomotic reconstructions (eg, evaluation for anastomotic leak and patency, bleeding, pouch formation)
- As an adjunct to minimally invasive surgery for the treatment of diseases of the colon and rectum
- Management or evaluation of operative adverse events (eg, dilation of anastomotic strictures)
- Foreign body removal
- Excision or ablation of lesions
- Decompression of acute megacolon or sigmoid volvulus
- Balloon dilation of stenotic lesions (eg, anastomotic strictures)
- Palliative treatment of stenosing or bleeding neoplasms (eg, laser, electrocoagulation, stenting)
- Marking a neoplasm for localization

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- Summary of proposed quality indicators for colonoscopy

Quality indicator	Grade of recommendation	Measure type	Performance target (%)
Preprocedure			
1. Frequency with which colonoscopy is performed for an indication that is included in a published standard list of appropriate indications, and the indication is documented	1C+	Process	>80
2. Frequency with which informed consent is obtained, including specific discussions of risks associated with colonoscopy, and fully documented	1C	Process	>98

Quality indicator	Grade of recommendation	Measure type	Performance target (%)
3. Frequency with which colonoscopies follow recommended post-polypectomy and post-cancer resection surveillance intervals and 10-year intervals between screening colonoscopies in average-risk patients who have negative examination results and adequate bowel cleansing (priority indicator)	1A	Process	≥90
4. Frequency with which ulcerative colitis and Crohn's colitis surveillance is recommended within proper intervals	2C	Process	≥90
Intraprocedure			
5. Frequency with which the procedure note documents the quality of preparation	3	Process	>98
6. Frequency with which bowel preparation is adequate to allow the use of recommended surveillance or screening intervals	3	Process	≥85 of outpatient examinations
7. Frequency with which visualization of the cecum by notation of landmarks and photodocumentation of landmarks is documented in every procedure (priority indicator)	1C	Process	
Cecal intubation rate with photography (all examinations)			≥90
Cecal intubation rate with photography (screening)			≥95

Quality indicator	Grade of recommendation	Measure type	Performance target (%)
8. Frequency with which adenomas are detected in asymptomatic average-risk individuals (screening) (priority indicator)	1C	Outcome	
Adenoma detection rate for male/female population			≥25
Adenoma detection rate for male patients			≥30
Adenoma detection rate for female patients			≥20
9a. Frequency with which withdrawal time is measured	2C	Process	>98
9b. Average withdrawal time in negative-result screening colonoscopies	2C	Process	≥6 min
10. Frequency with which biopsy specimens are obtained when colonoscopy is performed for an indication of chronic diarrhea	2C	Process	>98
11. Frequency of recommended tissue sampling when colonoscopy is performed for surveillance in ulcerative colitis and Crohn's colitis	1C	Process	>98
12. Frequency with which endoscopic removal of pedunculated polyps and sessile polyps <2 cm is attempted before surgical referral	3	Outcome	>98

Quality indicator	Grade of recommendation	Measure type	Performance target (%)
Postprocedure			
13. Incidence of perforation by procedure type (all indications vs colorectal cancer screening/polyp surveillance) and post-polypectomy bleeding	1C	Outcome	
Incidence of perforation—all examinations			<1:500
Incidence of perforation—screening			<1:1000
Incidence of post-polypectomy bleeding			<1%
14. Frequency with which post-polypectomy bleeding is managed without surgery	1C	Outcome	≥90
15. Frequency with which appropriate recommendation for timing of repeat colonoscopy is documented and provided to the patient after histologic findings are reviewed	1A	Process	≥90

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Endoscopic Retrograde Cholangiopancreatography (ERCP)

- Indicators
  - Indications for ERCP
  - Duct (CBD, PD)
    - Deep cannulation
    - Stones
      - Rates of success of extraction of stones < 10 mm
    - Stenting
      - Biliary obstruction
    - Post ERCP pancreatitis
    - Tracking of severe complications
    - Remediation, as appropriate

- Appropriate indications for ERCP
  - The jaundiced patient suspected of having biliary obstruction (appropriate therapeutic maneuvers should be performed during the procedure)
  - The patient without jaundice whose clinical and biochemical or imaging data suggest pancreatic duct or biliary tract disease
  - Evaluation of signs or symptoms suggesting pancreatic malignancy when results of direct imaging (e.g., EUS, US, computed tomography[CT], magnetic resonance imaging [MRI]) are equivocal or normal
  - Evaluation of pancreatitis of unknown etiology
  - Preoperative evaluation of the patient with chronic pancreatitis and/or pseudocyst
  - Evaluation of the sphincter of Oddi by manometry
  - Empirical biliary sphincterotomy without sphincter of Oddi manometry is not recommended in patients with suspected type III sphincter of Oddi dysfunction
  - Endoscopic sphincterotomy:
    - Choledocholithiasis
    - Papillary stenosis or sphincter of Oddi dysfunction
    - To facilitate placement of biliary stents or dilation of biliary strictures
    - Sump syndrome
    - Choledochocele involving the major papilla
    - Ampullary carcinoma in patients who are not candidates for surgery
    - Facilitate access to the pancreatic duct

- Stent placement across benign or malignant strictures, fistulae, postoperative bile leak, or in high-risk patients with large unremovable common duct stones
- Dilation of ductal strictures
- Balloon dilation of the papilla
- Nasobiliary drain placement
- Pancreatic pseudocyst drainage in appropriate cases
- Tissue sampling from pancreatic or bile ducts
- Ampullectomy of adenomatous neoplasms of the major papilla
- Therapy of disorders of the biliary and pancreatic ducts
- Faciliation of cholangioscopy and/or pancreatoscopy

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➢ Summary of proposed quality indicators for ERCP

Quality indicator	Grade of recommendation	Measure type	Performance target (%)
Preprocedure			
1. Frequency with which ERCP is performed for an indication that is included in a published standard list of appropriate indications and the indication is documented (priority indicator)	1C+	Process	>90
2. Frequency with which informed consent is obtained, including specific discussions of risks associated with ERCP, and fully documented	1C	Process	>98
3. Frequency with which appropriate antibiotics for ERCP are administered for settings in which they are indicated	2B	Process	>98

Quality indicator	Grade of recommendation	Measure type	Performance target (%)
4. Frequency with which ERCP is performed by an endoscopist who is fully trained and credentialed to perform ERCP	3	Process	>98
5. Frequency with which the volume of ERCPs performed per year is recorded per endoscopist	1C	Process	>98
Intraprocedure			
6a. Frequency with which deep cannulation of the ducts of interest is documented	1C	Process	>98
6b. Frequency with which deep cannulation of the ducts of interest in patients with native papillae without surgically altered anatomy is achieved and documented (priority indicator)	1C	Process	>90
7. Frequency with which fluoroscopy time and radiation dose are measured and documented	2C	Process	>98
8. Frequency with which common bile duct stones <1 cm in patients with normal bile duct anatomy are extracted successfully and documented (priority indicator)	1C	Outcome	≥90
9. Frequency with which stent placement for biliary obstruction in patients with normal anatomy whose obstruction is below the bifurcation is successfully achieved and documented (priority indicator)	1C	Outcome	≥90

Quality indicator	Grade of recommendation	Measure type	Performance target (%)
Postprocedure			
10. Frequency with which a complete ERCP report that details the specific techniques performed, particular accessories used, and all intended outcomes is prepared	3	Process	>98
11. Frequency with which acute adverse events and hospital transfers are documented	3	Process	>98
12. Rate of post-ERCP pancreatitis (priority indicator)	1C	Outcome	N/A
13. Rate and type of perforation	2C	Outcome	≤0.2
14. Rate of clinically significant hemorrhage after sphincterotomy or sphincteroplasty in patients undergoing ERCP	1C	Outcome	≤1
15. Frequency with which patients are contacted at or greater than 14 days to detect and record the occurrence of delayed adverse events after ERCP	3	Process	>90

N/A, not avalilable.

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Endoscopic Ultrasound

- Appropriate Indications for EUS
  - Staging of tumors of the GI tract, pancreas, bile ducts, and mediastinum including lung cancer
  - Evaluating abnormalities of the GI tract wall or adjacent structures
  - Tissue sampling of lesions within, or adjacent to, the wall of the GI tract
  - Evaluation of abnormalities of the pancreas, including masses, pseudocysts, and chronic pancreatitis
  - Evaluation of abnormalities of the biliary tree
  - Placement of radiologic (fiducial) markers into tumors within or adjacent to the wall of the GI tract
  - Treatment of symptomatic pseudocysts by creating an enteral-cyst communication
  - Providing access into the bile ducts or pancreatic duct, either independently or as an adjunct to ERCP
  - Evaluation for perianal and perirectal disorders (anal sphincter injuries, fistulae, abscesses)
  - Evaluation of patients at increased risk of pancreatic cancer
  - Celiac plexus block or neurolysis

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- Quality Indicators for EUS

Quality indicator	Grade of recommendation	Type of measure	Performance target (%)
Preprocedure			
1. Frequency with which EUS is performed for an indication that is included in a published standard list of appropriate indications and the indication is documented	1C	Process	>80
2. Frequency with which consent is obtained, including specific discussions of risks associated with EUS, and fully documented	3	Process	>98

Quality indicator	Grade of recommendation	Type of measure	Performance target (%)
3. Frequency with which appropriate antibiotics are administered in the setting of FNA of cystic lesions	2C	Process	N/A
4. Frequency with which EUS exams are performed by trained endosonographers	3	Process	>98
Intraprocedure			
5. Frequency with which the appearance of relevant structures, specific to the indication for the EUS, is documented	3	Process	>98
6a. Frequency with which all gastrointestinal cancers are staged with the American Joint Committee on Cancer (AJCC)/Union for International Cancer Control (UICC) TNM staging system (priority indicator)	3	Process	>98
6b. Frequency with which pancreatic mass measurements are documented along with evaluation for vascular involvement, lymphadenopathy and distant metastases	3	Process	>98
6c. Frequency with which EUS wall layers involved by subepithelial masses are documented	3	Process	>98

Quality indicator	Grade of recommendation	Type of measure	Performance target (%)
7a. Percentage of patients with distant metastasis, ascites, and lymphadenopathy undergoing EUS- guided FNA who have tissue sampling of both the primary tumor diagnosis and lesions outside of the primary field when this would alter patient management	1C	Process	>98
7b. Diagnostic rate of adequate sample in all solid lesions undergoing EUS-FNA (adequate sample is defined by the presence of cells/tissue from the representative lesion in question)	3	Outcome	≥85
7c. Diagnostic rates and sensitivity for malignancy in patients undergoing EUS-FNA of pancreatic masses (priority indicator)	1C	Outcome	Diagnostic rate: ≥70 Sensitivity: ≥85
Postprocedure			
8. Frequency with which the incidence of adverse events after EUS-FNA (acute pancreatitis, bleeding, perforation and infection) is documented	3	Process	>98
9. Incidence of adverse events after EUS-FNA (acute pancreatitis, bleeding, perforation and infection) (priority indicator)	1C	Outcome	Acute pancreatitis <2%Perforation: <0.5%Clinically significant bleeding: <1%

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Printed with permission: Wani S, et al. Quality Indicators for EUS. *Am J Gastroenterol* 2015;110:102-113.

ESOPHAGUS

GASTROESOPHAGEAL REFLUX DISEASE (GERD)

- Give 10 diagnostic tests for the diagnosis of GERD.

- Tests to assess reflux
  - Ambulatory intraesophageal pH monitoring
  - Ambulatory bilirubin monitoring (bile reflux)
  - Ambulatory esophageal impedance and pH monitoring
  - Barium esophagogram, video fluoroscopy swallowing study (VFSS)
  - Optical coherence manometry
  - Scintigraphy
  - Milk scan in infant

- Tests to assess **symptoms**
  - Empirical trial of acid suppression

			Sens, %	Spec, %
-	Heartburn and regurgitation	twice daily for 7 days	80	56
-	Noncardiac chest pain	twice daily for 14 days	75	85

Abbreviations: Sens, sensitivity; SPEC, specificity

  - Intraesophageal pH monitoring with symptom association analysis
  - Bernstein test (0.1 N HCl infusion to attempt to reproduce patient's typical symptoms)
  - Cortical sensing and motor control
  - Request® questionnaire

- Tests of **esophageal damage**
  - Endoscopy (optical white light EGD, capsule endoscopy [CE], EUS/FNA narrow band imaging [NBI] with zoom, chromoendoscopy)
  - Esophageal biopsy
  - Contrast radiography

Tests to assess **esophageal function**

- Esophageal manometry (normal or high resolution)
- Esophageal impedance
- VFSS

Abbreviations: CE, capsule endoscopy; EUS, endoscopic ultrasound; FNA, fine needle aspiration; GERD, gastroesophageal reflux disease; NBI, narrow band imaging; VFSS, videofluroscopy swallowing study

Adapted from: Richter JE. *Sleisenger & Fordtran's gastrointestinal and liver disease: Pathophysiology/Diagnosis/Management* 2006*:* pg. 916; and 2010, pg. 916.; Printed with permission: Murray JA. *Mayo Clinic Gastroenterology and Hepatology Board Review*: pg. 11.; Thomson ABR. *Clinical Medicine Gastroenterology* 2008;1:pg. 11.; and Spechler SJ. *2008 ACG Annual Postgraduate Course book*: pg. 113.

Clinical Trick

On any question where a correct response would include "endoscopy", mention additional forms of endoscopy, such as narrow band, zoom, and / or chromoendoscopy. And don't forget to mention to take a biopsy, and to perform therapeutic endoscopy, where appropriate.

- Diagnosis

Subtypes of GERD	Erosions on EGD	Abnormal pH - 1 m [1]	Symptom association [2]
Erosive reflux disease (35%)	+	+/-	+/-
Non-erosive reflux disease (40%)	-	+	+/-
Acid hypersensitive (20%)	-	-	+ (to acid reflux)
Non-acid hypersensitive (15%)	-	-	+ (to non-acid reflux)
Functional heartburn [3]	-	-	-

[1] pH-impedence monitoring
[2] symptom association, SI (symptom index) > 50%; SAP (symptom association probability) < 95%
[3] does not respond to PPI

Source: Savarino et al. Nat Rev Gastro & Hepatol 2013;10:371-380

- Clinical diagnosis

"The signs and symptoms are insufficient to establish a conclusive diagnosis of GERD, regardless of their frequency and intensity, resulting in a diagnostic certainty of around 40%"

	Heartburn and regurgitation in person > 54	Absence of heartburn
-	Sensitivity, 67%	33%
-	Specificity, 77%	24%
-	PLR, 2.83	NLR 0.44

Abbreviations: NLR, negative likelihood ratio; PLR, positive likelihood ratio

Source: Kim et al. 2008; 27:173-185.

- Typical GERD symptoms
  - Do not do conventional esophageal pH monitoring (proximal or distal)
  - Impedence pH metry (for non-acid or weakly acid reflux) contributes to the diagnosis in about 2 patients in 3 with atypical GERD symptoms
- Use of biopsies
  - In patients with GERD symptoms refractory to PPI OD for 4 to 8 weeks, the finding of widened intercellular spaces on light or electron microscopy "… increases the probability of diagnostic certainty and allows the analysis of the therapeutic response"
  - Basal cell hyperplasia (BCH) on esophageal mucosal biopsy has the following performance characteristics

    Sensitivity, 98% PLR 1.78

    Specificity, 45% NLR 0.04

  - Thus, the absence of BCH helps to exclude the diagnosis of GERD, or of active disease
- Investigation of associated disorders
  - Patients with the following conditions should be investigated for acid reflux, even in the absence of GERD symptoms
  - Pulmonary interstitial disease (idiopathic pulmonary fibrosis)
  - Chronic laryngitis

- Sleep disorders and / or sleep apnea
- Note:
  - There is a small ↑ risk of asthmatics (57%)
  - In asthmatics with symptomatic GERD. "…. the normal pH-metry can predict the absence of therapeutic response with PPI"

o Therapeutic test with PPI
- The definition of what is a "therapeutic test with PPI" is widely variable, e.g. dose and duration and outcome
- The wishy-washy best that guidelines can offer is to say that "in certain patients with suspected GERD, however, the diagnostic contribution of the therapeutic test with PPI is satisfactory"

➢ Natural history

NERD —(~20%)→ EE —worsening of EE→ BE

Abbreviations: BE, Barrett esophagus; ES, erosive esophagitis; NERD, non-erosive reflux disease

- Classify the drugs used to treat GERD.
  - sensation – TCA
  - ↑ saliva – chewing gum
  - ↑ LESP – cholinergic (bethanecol)
  - ↓TLESP – (GABA receptor agonist (baclofen)
  - ↓ coating – alginate, sucralfate
  - ↓acid – PPI, H_2RA, antacids
  - ↑ gastric emptying – prokinetics (e.g. domperidone)
  - ↓ bile acids cholestyramine sucralfate

- Give the **management** of gastroesophageal reflux disease.

➢ Confirm the diagnosis
  - Compatible symptoms and signs
    - Heartburn, dyspepsia, regurgitation
    - "extraesophageal" conditions in ear, nose, throat, lungs

- Laboratory
  - Iron deficiency ± anemia
  - Absence of eosinophilia
- Diagnostic imaging
  - Barium esophagogram
    - GER
    - Erosion / ulceration
    - Stricture
    - Hiatus hernia
    - Lower esophageal cancer
- Endoscopy (white band)
  - Who should have an EGD:
    - Depends upon which guideline is being followed
    - New symptoms age > 50 to 55 years
    - Alarm symptoms at any age
    - > 10 years of moderately severe symptoms occurring ≥ 3 times per week
    - Note: alarm symptoms have a very low PPV, but a NPV of ~98% for esophageal / gastric cancer
  - Normal, or grades LA A to D esophagitis
  - Complications
    - Stricture
    - Mass
    - Barrett esophagus / epithelium
    - Adenocarcinoma
  - Exclude other causes for symptoms
    - Other causes of esophagitis, e.g. EoE (eosinophilic esophagitis; about 5% of persons with refractory GERD may have EoE)
    - Peptic ulceration
    - Gastric ulceration
    - Gastritis outlet (e.g. H. pylori infection)
    - Gastric outlet obstruction
- Physiological studies*
  - Esophageal pH testing

- Esophageal manometry
  - 24 hr
  - 2 day BRAVO® study
- Esophageal pH and multichannel intraluminal impedence testing
- High resolution manometry (HRM)

* under special circumstances

- Histopathology
  - Normal
  - Reactive changes
  - Erosion / ulceration
  - Barrett epithelium (BE)
  - Adenocarcinoma

- Comorbidities
  - As in all medical conditions, psychological comorbidities need to be considered and managed where appropriate

- Lifestyle changes (LSC)
  - Evidence-based (EB)
    - Loss of excessive body weight
    - Elevation of head of bed (6 inches; or Styrofoam® wedge under the mattress) for nocturnal or laryngeal GERD symptoms
  - Case-by-case use
    - Diet
      - Avoid reflux-inducing foods, e.g.
        - Chocolate
        - Fatty foods
        - Peppermint
      - Avoid symptom-aggravating foods e.g.
        - Tomatoes
        - Citrus fruits
        - Colas
        - Red wine
        - Spices
      - Avoid bedtime snacks / meals
      - Avoid use of alcohol

- Position
  - Do not lie down for at least 2 hr after meals
- Salvation
  - Smoking – avoid tobacco products (↓ salvation)
  - Chewing gum
  - Oral lozenges
- Manage ascites
- Smoking cessation
- Refrain from eating 2 hours before lying down (after meals and at bedtime)
- Avoid (if possible) medications that worsen GER symptoms eg. (anticholinergics, benzodiazepines, beta-agonists, bisphosphonates, calcium-channel blockers, corticosteroids, estrogens, NSAIDs, opiates, progesterone, prostaglandins, theophylline)
- Nasal CPAP if obstructive sleep apnea is present
- Avoid exercise that may increase intra-abdominal pressure

Abbreviations: BMI, body mass index; CPAP, continuous positive airway pressure; GER, gastroesophageal reflux; GERD, gastroesophageal reflux disease

➢ Pharmaceutical measures

- **Acute therapy**
  - Used in addition to tailored life style changes
  - ↓ acid secretion (to intragastric pH > 4 for ~ 14 hours)
    - PPI > H2RA > antacids
      - Therapeutic gain (TG) 57% to 74% versus placebo for PPI, 10% to 24% for H_2RA for relief of heartburn and healing
      - Complete relief of heartburn, per week of Rx
    - Start with standard dose of PPI, taken 30 min before the first meal of the day, for 8 weeks (12% healing per week, but LA grade C or D [severe esophagitis] may take longer to heal)
      - Lower response of symptom of regurgitation to PPI / H2RAs (0 to 35%)
        - PPI 12%
        - H_2RA 6%
      - If symptom response to PPI is incomplete after 8 weeks of od therapy, increase to bid therapy, standard dose 30 min before breakfast and supper (on patient-by-patient basis; not supported by systemic review)

        - The ↑ therapeutic gain for doubling the dose of PPI is
            - Symptom improvement 4%
            - Healing 6%
        - In some persons, switching to another PPI may prove to be useful; this is a clinical observation, and the explanation for this phenomenon is not clear
    - ↑ rate of gastric emptying
        - Use a prokinetic as adjunctive therapy of incomplete response to PPI bid for patients with possible delayed gastric emptying contributing to their poor therapeutic response
    - There are concerns now of po domperidone causing ventricular arrhythmia and sudden cardiac death (SCD)
    - Avoid in patients with heart failure or history of arrhythmias
    - Corrected QT must be normal on ECG (no QT conduction defect through smooth muscle receptor) when using prokinetics
    - Any drug potent enough to alter GI motility will affect the heart – same effects on smooth muscle
    - Don't combine erythromycin and domperidone for gastroparesis (both CYP 3A4 inhibitors)
    - ↓ TLESR
        - Baclofen (gamma-aminobutyric acid agonist for the type B receptors) may be used in refractory GERD
            - 10 mg bid, increasing slowly to 20 mg tid, or maximum benefit obtained without the development of CNS-related adverse effects

SO YOU WANT TO BE A GASTROENTEROLOGIST!

- Give the mechanisms of action of **gabba β receptor agonists** (e.g. baclofen) on the physiology of the esophagus and stomach which make this class of drugs potentially useful in persons with refractory GERD symptoms.
    - Gabba β receptor agonists have the following physiological effects
        - ↓ TLESR (~50%)
        - ↑ LESP (basal)
        - ↑ rate of gastric emptying
        - ↓ reflux episodes (~40%)

Abbreviations: LESP, lower esophageal pressure; TLESR, transient lower esophageal pressure relaxation

- ↓ H. pylori infection
  - Some algorithms for the management of uninvestigated dyspepsia support a therapeutic trial of empiric PPI therapy, or empiric anti-pylori therapy, or “test-and-treat” H. pylori infection.
  - Without EGD plus biopsy, it is not possible to determine if the H. pylori-associated gastritis was
    - Increasing intragastric pH (hypoacidia as a result of pangastritis), or
    - Decreasing intragastric pH (hyperacidia as a result of antral gastritis, and thereby a possible contribution to GERD symptoms)

- **Maintenance therapy**
  - Continuous therapy
    - If recurrent typical symptoms within ‘ 3 months after stopping acute Rx
    - Use half the standard dose if od PPI was effective for acute Rx, and full single standard dose if bid PPI was necessary
  - Repeat acute therapy
    - If recurrent typical symptoms in 3 months
    - This provides for a trial off medications, to determine each person`s individual natural history
  - Intermittent, “on demand”
    - On demand therapy has been validated only for endoscopically investigated dyspepsia, and not for “uninvestigated dyspepsia”.
    - Only for mild to moderate heartburn in the patient having had an EGD showing only mild or no esophagitis.
  - LA C & D (severe esophagitis)
    - May take 8 rather than 4 weeks to resolve symptoms / heal severe esphagitis
    - More likely to quickly relapse off x
    - Maintenance dose usually that dose which was initially required for healing
    - Not suitable for “on-demand” therapy

- Surgery
  - Surgery is an effective option for the management of GERD, but only in highly selected patients
  - The general standard of care is for the person with GERD who is being considered for a surgical procedure (e.g. fundoplication) to have at least esophageal manometry, and preferably also esophageal pH and multichannel intraluminal impedence testing.

- Give 5 indications for open or laparoscopic surgical fundoplication in the patient with GERD.
  - GERD symptoms responding to PPI (penalty for "failure of PPI" as an indication)
  - Intolerance to PPIs
  - Cost of PPIs
  - Young person (concern for adverse effects of PPIs,and risks of longtern use)
  - Patient preference (desire for a "cure")
  - Persistent large volume regurgitation
  - Large symptomatic hiatus hernia
  - Respiratory complications from recurrent aspiration
  - Recurrent peptic strictures in a young person

Abbreviations: GERD, gastroesophageal reflux disease; PPI, proton pump inhibitor

- Endoscopic therapy
  - Radiofrequency energy delivery to the gastro-esophageal junction (the Stretta procedure) improves gastro-esophageal reflux disease (GERD) symptoms and quality of life.
  - This was accompanied by a decrease in compliance of the gastro-esophageal junction.
  - The decrease in compliance was not due to fibrosis, as it was reversible by smooth muscle relaxants.

Source: Arts J, et al. Am J Gastroenterol 2012; 107: 222-230.

- **Special Considerations**

➢ Pregnancy and lactation

  - PPIs and H_2RAs should only be used when life style changes fail
  - Do not confuse dyspepsia / heartburn with pregnancy-associated nausea and vomiting
  - These drugs have category 'B' in the FDA classification, except for omeprazole, which is 'C'.
  - If a recurrence of symptoms occurs within 1 year, it will usually develop within the first 3 months

- Give the FDA category for the safety of drugs used to treat GERD in pregnancy and recommendations for breast-feeding.

Drugs	FDA category	Recommendations for breast-feeding
○ *Antacids*		
- Aluminum-, calcium or magnesium-containing antacids	None	Most are safe for use during pregnancy and for aspiration prophylaxis during labour because of minimal absorption Avoid long-term, high-dose therapy in pregnancy
- Magnesium trisilicates	None	Not safe for use in pregnancy as cause fluid overload and metabolic alkalosis
- Sodium bicarbonates	None	No teratogenecity in animals. Generally regarded as acceptable for human use because of minimal absorption
○ *Mucosal protectant*		
- Sucralfate	B	A prospective, controlled study suggests acceptable for use in humans

Drugs	FDA category	Recommendations for breast-feeding
○ *Histamine2-receptor antagonist (H2RA)*		
- Cimetidine	B	Same as above. Ranitidine is the only H2RA whose efficacy during pregnancy has been established
- Ranitidine	B	Same as cimetidine, but paucity of safety data in humans
- Famotidine	B	Not recommended during pregnancy. In animals, spontaneous abortion, congenital malformations, low birth weight and fewer live births have been reported.
- Nizatidine	B	Little data in humans.
○ *Promotility agents*		
- Cisapride	**C**	Embryotoxic and fetotoxic in animals. Prospective controlled study in human suggest acceptable in pregnancy, but was removed because of cardiac arrhythmias
- Metoclopramide	B	No teratogenic effects in animals or humans reported Embryotoxic and fetotoxic in animals. Case reports in human suggest similar concerns. Possible cardiac damage.
○ *Proton-pump inhibitors*		
- Omeprazole	**C**	For all PPIs, no teratogenicity or harm, but only limited human pregnancy data
- Lansoprazole	B	
- Rabeprazole	B	
- Pantoprazole	B	
- Esomeprazole	B	

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- **Nocturnal acid breakthrough (NAB)**
  - Definition: intragastric pH<4 for >60 min during the night time
  - NAB may be more frequent in GERD plus BE
  - Poor correlation between NAB and nocturnal heartburn
  - In specific, the occasional patient with nocturnal heartburn despite bid PPI may respond to the addition, as adjunctive therapy, of an H_2RA.
  - Because of high likelihood of the rapid development of tolerance to an H2RA, if the patient continues to have symptoms at night despite PPI bid, H2RA may be helpful when given intermittently or on demand

Clinical Alert
When a patient is suspected as having NAB (nocturnal acid breakthrough), the PPI and the H_2RA must not be given concurrently, because this reduces the acid inhibitory effect of each. When an H2RA is given intermittently for NAB, it is usually effective. However, if H2RA are taken daily, tachyphylaxis develops and the initial benefir of H2RA is lost.

- **Refractory GERD**
  - GERD is said to be refractory if the patient's symptoms have not responded to their "satisfaction" after a 4 week curse of PPI, taken once or twice a day.
  - The definite is based on subjective reporting of symptoms, and is not standardized in terms of which symptom(s), dose and duration of PPI use, naïve or pretreated patients, uninvestigated or investigated dyspepsia etc.
  - For example, the response rate of NERD (normal endoscopy reflux disease) to PPIs is only about 60% as that for erosive esophagitis.
  - About half of symptomatically refractory GERD patients have "functional heartburn"
  - Therapeutic options for refractory GERD symptoms, after confirming the diagnosis of GERD, and confirming that the patient is taking the PPI Rx 30 min before breakfast and dinner, include:
    - Prokinetics
    - Baclophen

- H2RA intermittently or on demand at bedtime
- Antacids, barrier agents (e.g. Gaviscon®)
- Bile salt binders
  - Sucralfate
  - Cholestyramine
  - Pain modulators (anti-depressants in low, non-mood-altering doses)
    - SSRI (selective serotonin reuptake inhibitors)
    - TCAs (tricyclic antidepressants)
    - Trazadone
  - Acupuncture
  - Hypnosis

- Outline the possible empiric medical trial for **GER-related cough**.

➢ Medications

- Twice daily PPIs 30-60 minutes before breakfast and dinner
- Consider adding a prokinetic agent initially if dysphagia is present or if cough does not improve with PPI
- Assess response to therapy within 1-3 months
- Lifestyle modifications (please see question 10, page 20)

➢ Further testing

Abbreviations: GER, gastroesophageal reflux; PPI, proton pump inhibitor

Adapted from: Chandra KM and Harding SM. *Nat Clin Pract Gastroenterol Hepatol* 2007; 4(11): 606.

➢ **Rebound Acid Secretion** ("Acid Rebound")

- Definition: An increase in acid secretion to above pretreatment values when an anti-secretory drug (e.g. PPI, H2RA) is suddenly discontinued.

- The amount and duration of use of anti-secretory drug influence the magnitude of the acid rebound, which is usually ~15%, which may be sufficient to cause a post-treatment recurrence of symptoms.

- Give the **pathophysiological mechanism(s)** for the phenomenon of acid rebound which occurs when anti-secretory treatment is suddenly stopped.

  - Acid secretion inhibition → ↑ gastrin
    → Up-regulation (hypertrophy / hyperplasia) of
      - Parietal and G cells (in antrum and on pancreatic islet cells), as well as other ECL cells
      - Ach pathways
    → Down-regulation of D-cells
  - Suddenly stopping PPIs
    - A given stimulus causes more release of gastrin and Ach (acetylcholine), more parietal cells to be stimulated by Ach and gastrin, and less down regulation of acid secretion from somatostatin inhibition of somatostatin (relative loss of inhibition and gain of secretion)

Notes from Guidelines

➢ Management

- PPI od or bid
  The clinical response in most patients is similar to once or twice a day PPI (od, bid respectively)
- Note, however the cases of acid reflux and extraesophageal manifestations of GERD (asthma, bronchial hyperactivity, laryngitis and non-cardiac thoracic pain-cardiac thoracic pain) respond better to a double dose of PPI for longer periods (2 to 6 months)
- The duration of therapy with PPI od for GERD is 4 weeks, although in some patients who remain therapeutic failures, the treatment can be extended to 8 weeks.
- Adding H2RA to PPI for nocturnal symptoms
  - While some patients may respond in the short term to the addition of an H2 receptor antagonist to PPI, tachyphylaxis may develop leading to loss of this beneficial effect.
  - Used in their recommended doses, the PPIs are clinically equivalent for symptom relief and for healing, and this benefit is not conclusively enhanced with the use of a prokinetic.
  - “half dose” PPI for 6 months maintains remission in about 80% of GERD patients, and there are no clinically important differences

- In the patient with GERD symptoms but no erosions shown on GERD (NERD, non-erosive GERD), PPI may be taken as needed for up to 6 months
- Note: when considering the use of "on demand" PPI maintenance therapy, the patient must have had a recent normal EGD, and use the prn PPI for no more than 6 months.
- While life-style changes may benefit some patients with GERD, and may have many other health benefits (e.g. weight reduction, stop smoking, moderation of alcohol intake), the strength of evidence in not always strong for their use in GERD.
- The initial benefit of surgery for GERD declines over time, and the durations of follow-up are not considered to be sufficiently long to declare surgery vs. PPI the optimal long-term treatment for GERD.

Source: Moraes-Filho et al., Arq Gastroenterol 2010; 47: 99-115; Agency for healthcare Research Quality, Comparative Effectiveness Review, # 29.

BENIGN ESOPHAGEAL STRICTURE

- Give 5 etiologies of benign, non-GERD related esophageal strictures.
  - Congenital—strictures, atresia
  - Drugs and chemicals—radiation, caustic, chemical, thermal, quinidine gluconate
  - Webs, rings
  - Sclerotherapy
  - Acid and non-acid causes of esophagitis
  - Surgery--complicated reflux strictures (NG tube, ZE syndrome), ischemia, anastomotic (staples)
  - Iatrogenic - EMR for BE, prolonged NG tube, therapy, PDT

Abbreviations: BE, Barrett's epithelium; EMR, endoscopic mucosal resection; NG, nasogastric tube; PDT, photodynamic therapy; ZE, Zollinger-Ellison syndrome

- Give 4 predictors of initial therapeutic failure of pneumatic dilation of benign esophageal strictures (i.e. repeated dilations required).

➢ Related to patient
  - Age <40 years
  - Male
  - Dilated esophagus

➢ Related to procedure
  - Inadequate dilation
    - Small size balloon (30 mm)
    - LES pressure >10 mm Hg post-dilation
  - Poor esophageal emptying post-treatment

Abbreviation: LES, lower esophageal sphincter

Adapted from: Boeckxstaens GEE. *Best Pract Res Clin Gastroenterol* 2007;21(4): 595.

ESOPHAGEAL RINGS

- Give 7 features distinguishing a type A (Schatzki ring) from type B esophageal ring.

	Type A	Type B
○ Encircle the lumen	– Yes	▪ Yes
○ Esophageal vestibule	– Proximal	▪ Distal
○ Composition	– Muscular	▪ Mucosa, submucosal
○ Thickness	– Thick, ~ 5 mm	▪ Ach pathways ▪ Thin ~ 2 mm
○ Aperture	– < 13 mm	▪ ≥ 13 mm
○ Mucosal covering	– Squamous, upper & lower	▪ Squamous – upper ▪ Columnar – lower
○ Frequency	– Rare	▪ 4%
○ Symptoms	– No	▪ Yes
○ Presence of hiatus hernia	– Occasional	▪ Always
○ Location	– Upper end, LES	▪ Lower end, LES*

*junction of the vestibule of the esophagus, and the gastric cardia

SO YOU WANT TO BE A GASTROENTEROLOGIST!

It is recognized that some patients with a Schatzki ring have symptomatic gastroesophageal reflex disease (GERD), almost all have a hiatus hernia, but only a modest proportion have erosive esophagitis.

- Give the explanation for this observation.
  - The ring in the lower esophagus prevents acid exposure to the more proxima portions of the esophagus, reducing the risk of mucosal damage.
- Give the role of PPI therapy in the patient with a Schatzki ring.
  - PPIs reduce the need for repeat esophageal dilation by 40% over 35 months.

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- Give the anatomical difference between an esophageal ring (ER) and an esophageal web (EW).

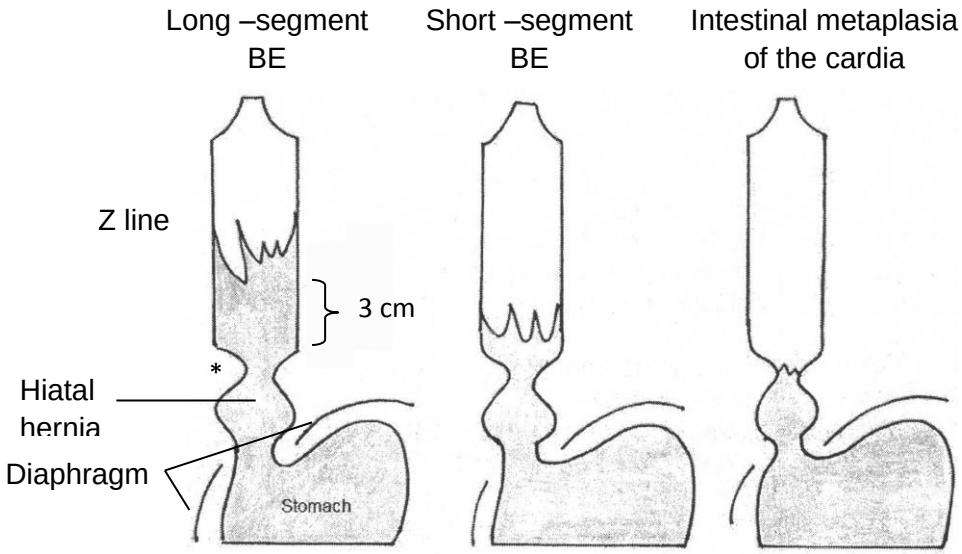
	ER	EW
○ Location	– Cervical esophagus	▪ Esophageal vestibule
○ Encircle the lumen	– Yes	▪ No (anterior wall of esophagus, extending to lateral but not to posterior wall)
○ Symptomatic	– 95%	▪ May be asymptomatic
○ ↑ risk of cancer	– Yes, adenocarcinoma	▪ Yes, squamous carcinoma

- In the setting of the patient with the sensation of a lump in their throat (globus), define heterotropic gastric mucosa (HGM) (inlet patch), and reasons for taking biopsies from the HGM.
  - HGM is a small, clearly defined patch of salmon-pink mucosa seen taking a mucosal just below the upper esophageal sphincter, and is comprised of gastric fundic or antral-type mucosa
  - When the HGM is lined by chief or parietal cells, it may be infected by H. pylori, may ulcerate, may cause a web or stricture, or be complicated by adenocarcinoma

RUMINATION SYNDROME

- Definition
  - "Effortless, often repetitive regurgitation of recently ingested food into the mouth".
  - Retrograde flow of gastric contents into the esophagus is due to contracting the abdominal muscles and subsequent increase in intragastric pressure.
  - The regurgitated material may be chewed and swallowed again or may be spat out.

BARRETT ESOPHAGUS (BE)



  - Patients with long segment or short segment BE have salmon-coloured mucosa extending up into the tubular esophagus
  - Biopsy shows intestinal metaplasia with goblet cells
  - If intestinal metaplasia with goblet cells is found at a normally located zig zag line (Z line), the patients has intestinal metaplasia of the cardia, which confers a lower cancer risk.

*End of tubular esophagus and beginning of stomach.

Adapted from: Mayo GI page 23.

Clinical Pearl

There are a number of expensive endoscopic techniques which may increase the accuracy of diagnosis of Barrett epithelium (BE) by highlighting sites of greater likelihood for obtaining "positive histopathological diagnosis".

- Don't forget the simplest trick
  - Clearing mucus from the esophagus with water flushes containing 1% acetylcysteine.

Clinical Gems

- Sapphire: While use of the Prague C & M criteria for the endoscopic grading system for Barrett esophagus has been validated, it remains to be confidently confirmed that this has more than descriptive value.
  - Nonetheless, if this is a standard of care in your practice community, "go with the flow".
- Emerald: Most BE neoplasia is at the "12 to 6 o'clock" position in the endoscopic view with the patient in the left lateral position, so take a good second look in this area.

- Give the **Seattle protocol** which is recommended for taking esophageal mucosal biopsies for Barrett esophagus (BE).
  - Visible abnormalities
    - Multiple biopsies to be targeted to this area
  - All other areas
    - Four-quadrant biopsies from the top of the gastric folds, proximally for every 1 cm to the squamocolumnar junction (the upper most part of the BE)
  - Note:
    - Taking esophageal mucosal biopsies at 2 cm rather that at 1 cm intervals will miss half of the neoplasias.
    - Targeted biopsies will yield ~80% of BE lesions.
    - Put biopsies from the various 1 cm levels in separate pathology sample bottles.

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- Give 4 molecular tests which may suggest the presence of dysplasia in Barrett Esophagus.
  - DNA aneuploidy
  - Ki67 (proliferation) – increased expression on immunohistochemistry
  - Oncogenes – cyclin D1, TGFα, EGFR, Rus, B-catenin
  - Tumour suppressors genes
  - Anti-apoptosis genes
  - Anti-senescence markers - telomerase

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- Endoscopic ultrasound (EUS) in BE
  - High frequency miniprobes
    - Provide better visualization and resolution of the mucosa than does EUS and therefore to T-staging in BE, but gives poorer visualization of deeper areas, and thus less reliable N-staging.
    - The deeper the depth of the HGD / EC (high grade dysplasia / esophageal cancer), the greater the likelihood of metastasis to lymph nodes.
  - EUS
    - Has greater value for identifying lymph node involvement (metastasis) (N (nodal)-staging)
    - NPV (negative predictive value) > 95%

- Give 3 endoscopic resection (ER) techniques for BE.
  - EMR (endoscopic mucosal resection)
    - Submucosal lifting, followed by endoscopic resection-cap technique (radical ER)
    - "suck-band-and ligate" (snare)
    - MBM (multiband mucosectomy)
  - ESD (endoscopic submucosal dissection)

Note: Consider using standard dose PPI bid for 3 to 6 weeks after ER to allow for regrowth of squamous epithelium and healing of any post-ER defects in the mucosa.

- Success of EMR for BE

Timing	Complete eradication: Neoplasia	Complete eradication: Metaplasia
Initial	98%	85%
Follow-up (19 to 49 months)	95%	81%

  - Recommended surveillance
    - First year after EMR, q 3 month
    - Subsequently, q 1 year

- Give the factors which influence the **rate of remission** after endoscopic resection for HGD or EC, as well as those factors which influence the rate of recurrence (or development of metachronous malignancies).

- Higher rate of remission (59% to 99%)
  - Macroscopic characteristics

Macroscopic characteristics	Type
Protruded	I
Flat, elevated	IIa
Flat	IIb
Flat, depressed	IIc

    - Success: I > IIa > IIb > IIc
  - Size
    - < 20 mm
  - Differentiation
    - Well to moderate differentiation > poor differentiated (univariate, but not multivariate analyses)

Abbreviations: EC, esophageal cancer; HGD, high grade dysplasia

Useful background: **Risk of serious complications of EMR** for BE (even when performed by experienced endoscopists):

- Bleeding – 0% to 46%
- Perforation – 1% to 5%
- Strictures – 2% to 88%
- Recurrence – ~ 20%

- High rate of recurrence (7% to 30% within 5 years)
  - Lesion
    - Macroscopic features
      - ↑ diameter of lesion
      - ↑ length of BE
    - Microscopic
      - Residual dysplasia
      - Multifocal neoplasia
  - Treatment
    - Piecemeal resection
    - Monotherapy (ER without adjunctive ablative therapy, i.e. not using combined therapy)
      - PDT (photodynamic therapy)
      - APC (argon plasma coagulation)
      - RFA (radiofrequency ablation)
    - > 10 month to achieve remission

PROTON PUMP INHIBITORS (PPI)

- The proton pump
  - The proton pump is comprised by the H^+ - K^+ - ATPase in the canalicular membrane at the apical surface of the parietal cell.
  - The H^+ - K^+ - ATPase is a member of the P2 family of ion motive transport enzymes.
  - The secretory canaliculus is an acidic space in a slightly invaginated area of the apical membrane of the parietal cell.
  - The absorbed PPIs accumulate in this acidic space in the secretory canaliculus.
  - The PPIs are weakly protonatable pyridines, with values of pKa ~4, depending on the individual PPI.

- The higher the value of the pKa, the faster the PPI undergoes an acid-catalyzed conversion to the active agent, a thiophilic sulfonamide.
- The thiophilic sulfonamide forms a non-reversible disulfide bond with cysteine 813 in the activated H^+ - K^+ - ATPase in the canaliculus and apical membrane of the parietal cell.
- Cysteine 813 is in the catalytic alpha-subunit of the H^+ - K^+ - ATPase.
- While all PPIs bind to cysteine 813, some PPIs may bind to additional cysteine molecules (e.g. pantoprazole also binds to cysteine 822).
- The resulting non-competitive inhibition in the final common pathway of the parietal secretion of HCl lasts until new pumps and produced in new parietal cells.
- This explains why the serum half-life (T1/2) of PPIs is about 60 min, but the biological T1/2 is about 14 hr.

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Caucasian race	CYP2C19 gene	Polymorphisms	Duration of ↓ H^+ with PPIs
5%	Inactivating mutation	Slow (↓ rate)	Long
~65%	Wild type gene	Rapid (↑ rate)	Short

- In the context of PPIs, give the advantages and disadvantages of **polymorphisms** for a mutation in **CYP2C19**.

	Clinical Advantage	
	H.pylori eradication	GERD
○ Homozygous CYP2C19 mutation (slow metabolizers)	100%	85%
○ Heterozygotes	60%	68%
○ Homozygous, wild type (rapid metabolizers)	29%	16% (severe)

  - CYP2C19 mutation and saturation
    - Adverse interactions with
      - Clopidogrel, Diazepam, Phenytoin, Theophylline , Warfarin

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- Give the explanation why the PPI rabeprazole has fewer adverse effects (AEs) than omeprazole, and why pantoprazole has even fewer risks.
  - Omeprazole is metabolized by **CYP2C19**, and depending upon whether the patient is a deficient or saturated phenotype, the PPI may interfere with the metabolism of many drugs.
  - Rabeprazole has affinity for **CYP2C19 plus CYP3A4**, so the risk of adverse effects from drug interactions is less.
  - Pantoprazole is rapidly **sulfated** after CYP2C19 methylation, so it does **not** induce CYP3A4 or CYP1A, and thus has a much lower potential for AEs than do the other PPIs.

➢ Metabolism

- Give 15 **indications** for the use of PPIs

  - Esophagus
    - Symptoms and / or signs of damage from acid-related disorders
    - NERD (non-erosive reflux disease)
    - GERD, including BE
    - Tracheopulmonary ("supraesophageal") disorders associated with GERD
    - EoE [eosinophilic esophagitis]
    - Motility disorders
      - Achalasia
      - Scleroderma
      - DES / hypertensive esophagus
    - Prevention or reduction of damage of aspiration pneumonitis
    - ↓ # of esophageal dilations needed to relieve dysphagia from benign (peptic) stricture

  - Stomach
    - PUD (peptic ulcer disease, including GU [gastric ulcer] and DU [duodenal ulcer] caused by ASA / NSAIDs, H. pylori and idiopathic ulcer disease.
    - H. pylori eradication (with antibiotics)
    - Hypersecretory states (e.g. ZES [Zollinger Ellison Syndrome])

- Prevention of drug-induced damage to stomach
  - ASA
  - NSAIDs
  - COXIBs
- Prevention of "stress" ulcer disease

- Small bowel
  - ↓ drainage from upper GI fistula
  - Short bowel syndrome
  - ↓ small bowel output
  - Prevention of stress ulceration
  - Bleeding Meckel diverticulum

- Pancreas
  - ↓ Pain from pancreatitis
  - ↑ Enzyme replacement effectiveness (↓ acid-induced breakdown of enzyme replacement therapy)

Adverse Effects of PPIs

- Give 8 **potential risks** of longterm PPI therapy.

	Risk magnitude/possible consequence
Associated with hypergastrinemia	
- Hypergastrinemia-induced carcinoid tumours	▪ Not demonstrated in humans
- Accelerated progression of atrophic gastritis/gastric cancer with concomitant *H. pylori* gastritis	▪ No documentation of an increase in atrophic gastritis and no basis to recommend testing or treatment for *H Pylori* before longterm PP use
- Formation of gastric fundic gland polyps	▪ Odds ratio of 2.2 for developing Fundic gland polyps within 1-5 years, negligible, if any, risk of dysplasia ▪ Some patients show decreased vitamin B_{12} levels after years of acid inhibition, case reports (2) of clear deficiency

Risk magnitude/possible consequence

- Malabsorption
  - Vitamin B_{12} malabsorption
    - Nested case-control study of UK patients older than 50 years; adjusted odds ration of 1.44 (95% confidence interval, 1.30-1.59) of hip fracture with PPI use longer than 1 year
  - Calcium malabsorption / metabolic bone disease
    - Fractures
    - OR
    - Hip 1.30
    - Spine 1.56
    - All sites 1.16
    - While there is an ↑ relative risk of metabolic bone disease in persons who use PPI > 2 years, the ↑absolute risk is small:

Absolute risk of hip fractures per 1000 person-years	
PPI non-users 1.51	Regular PPI users 2.02

- Infection
  - Increased risk of *C difficile* colitis
    - PPI use is independent risk of *C difficile* diarrhea in antibiotic users, odds ratio of 2.1 (95% confidence interval, 1.2-3.5)
    - There is an ↑ risk of enteric infections in persons on PPI, this includes C.difficile, Campylobacter, Salmonella, and Traveller's Diarrhea/
    - The ↑ risk of Clostridium difficile infection associated with the use if PPIs occurs even in persons who have not previously taken antibiotics.
    - ↑ risk with use of PPIs (or odds ratio)

	OR
– C.difficile infection	
▪ Incident	1.7
▪ Recurrent	2.5
– CAP / HCAP	1.27

	Risk magnitude/possible consequence
- Increased risk of community-acquired or nosocomial pneumonia (presumably aspiration)	▪ Nested case-control analysis, adjusted odds ratio for pneumonia with PPI use of 1.73 (95% confidence interval, 1.33-2.25) ▪ OR of CAP / HCAP, 1.27

Abbreviations: CAP, community acquired pneumonia; HCAP, healthcare associated pneumonia

- Drug-drug interactions; PPIs metabolized by cytochrome P450 and may induce or inhibit drug metabolism (phenytoin, warfarin, Plavix®)
  - Clinically significant PPI drug-drug interactions are rare (<1/million prescriptions)
  - PPIs reducing the effectiveness of clopidogrel
  - Not proven

○ Cancer	- Do not increased risk of gastric cancer is only a theoretical consideration: ▪ Gastric colonization with bacteria that convert nitrates to carcinogenic *N*-nitroso compounds - Data on PPI use and increased gastric *N*-nitrosamine remain uncertain and the risk of cancer is speculative.
○ Safety in pregnancy (Omeprazole crosses placenta and is pregnancy safety category C; other PPIs are category B)	- Based on 345 accidental exposures compared with 787 controls, no observed increased teratogenicity
○ Miscellaneous	
- Collagenous colitis	▪ Extremely rare
- Anaphylaxis	▪ Extremely rare
- Acute interstitial nephritis	▪ 64 cases worldwide, partially reversible (one case required dialysis; no deaths), estimated risk 1/12,500 patient-years of PPI therapy)
- Pancreatitis	▪ Extremely rare

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The acid inhibitory effect of a single dose of PPI is less than the inhibitory effect, which occurs after multiple dosing.

- Give the explanation for the **steady-state phenomenon** of the use of PPIs.
    - When food enters the stomach, not all the parietal cells become active.
    - PPIs only bind to the cysteine 813 of H^+ - K^+ - ATPase when the parietal cell H^+ - K^+ - ATPase is active.
    - Over several days, more and more parietal cells will have been stimulated, resulting in more and more proton pump being activated and subsequently inhibited by the PPI.
    - In the same manner as the effect of the progressively increased recruitment of H^+ - K^+ - ATPase and its inhibition by PPIs, the acid inhibitory effect of the PPIs may last 1 to 2 days after the PPI has been stopped.

There are differences between PPIs in terms of their pKa, rate of absorption and metabolism, including differences in PK (pharmacokinetics) and PD (pharmacodynamics) properties

- Give the regimens for "**hepatic dosing**' or "**renal dosing**" of PPIs in persons with cirrhosis or renal insufficiency, and in persons on certain HIV protease inhibitors.
    - PPIs do not require either hepatic- or renal- dosing
    - PPIs reduce the absorption of some protease inhibitors (PPIs used for HIV and HCV infections), so the dose of the PPIs may need to be increased.

- Give the influence of H. pylori infection on the **PPI-associated risk** of developing atrophic gastritis (gastric atrophy; atrophy of gastric glands) in the body of the stomach.
    - PPI use and annual incidence of atrophy of the mucosa of the gastric body (AMGB)

	H. pylori	AMGB
–	Positive	4.7
–	Negative	0.7

Thus, the risk of gastric atrophy resulting from the long-term use of PPIs occurs mainly in persons who are H. pylori positive.

The malabsorption of iron and vitamin B12 in persons taking PPIs chronically may not necessarily be clinically significant. However, the malabsorption of calcium and reduction in osteoclastic activity with PPIs is associated with an ↑ risk of osteopenia and osteoporosis.

- Give the physiological explanation why some cardiac patients with heart failure who are chronically taking PPIs require **monitoring of their serum magnesium (Mg^{2+})** concentration.

    - PPIs lower the serum concentration of Mg^{2+}, as also do diuretics and digoxin, placing persons consuming PPIs at risk of the adverse effects of hypomagnesemia.

- Give 3 acid-related disorders and their therapeutic intragastric pH target.

	pH (% pH ≥ n)	Duration of treatment, wks
○ DU*	3	4
○ GERD	4	4-8
○ H. pylori	5	1-2
○ NVUGIB**	6	3 days

* the usual duration of treatment of DU is 4 weeks, and 8 to 12 weeks for gastric ulcer (GU), but the pH target (% pH ≥ x) is not known for GU.

** Initially IV PPI for 3 days, followed by oral PPI for a period depending upon the etiology of the NVGIB

Abbreviations: DU, duodenal ulcer; GERD, gastroesophageal reflux disease; GU, gastric ulcer; NVUGIB, non-variceal upper GI bleed

EOSINOPHILIC ESOPHAGITIS

- Definition
    - Eosinophilic esophagitis, ≥ 15 eosinophils in 2 HPFs (high power fields)
    - Eosinophilic microabscesses, ≥ 4 eosinophils in aggregation
    - Note: PPI responsive eosinophillic esophagitis (EoE) is a subtype of EoE

- Demography
  - Eosinophilic esophagitis (EoE) is more common among males and Caucasians.
  - Caucasians are
    - Older at diagnosis with eosinophilic esophagitis (EoE) than are African Americans
    - Less likely to present with failure-to-thrive
    - More likely to have esophageal rings
  - Males were more likely to be diagnosed in childhood and more frequently report dysphagia or food impaction.

- Clinical

- Give the typical presentation of eosinophilic esophagitis.
  - Young adult
  - Male to female ratio of 3:1
  - Intermittent dysphagia, sometimes severe
  - Food impaction
  - Failed treatment with proton pump inhibitor (PPI) therapy for presumed GERD
  - Chest pain with odynophagia
  - Peripheral eosinophilia is common
  - Atopic diseases

Printed with permission: Attwood SEA, and Lamb CA. *Best Pract Res Clin Gastroenterol* 2008;22(4): 641.

- Diagnosis
  - The diagnosis of EoE should be suspected in the young patient with
    - Solid food impaction
    - Atopy
    - GERD symptoms
  - Sometimes only partially responsive to PPI for 2 months
    - Typical EGD changes of EoE

- Pathology
  - "the findings of eosinophils in the squamous epithelium of the esophagus, is abnormal and the underlying cause should be identified
    - Eosinophilic syndromes
    - Isolated esophageal eosinophilia
      - PPI responsive GERD (acid mediated)
      - PPI-REE Non-GERD (non-acid mediated)
      - EoE Immune mediated
  - To diagnose EoE requires ≥ 4 esophageal mucosal biopsies, 2 from distal and 2 from mid-proximal esophagus, with ≥ 15 eosinophils / hpf which persist after a trial of PPI
  - "At the time of initial diagnosis, biopsies should be obtained from the [gastric] antrum and / or duodenum to rule out other causes of esophageal eosinophilia in all children and in adults with gastric or small intestinal symptoms or endoscopic abnormalities
  - Intermittent, solid food dysphagia in EoE is typical
  - Basal cell hyperplasia is more common in EoE than in GERD
  - Eosinophils are closer to surface of esophagus in EoE than in GERD
  - ↑ eosinophils in esophagus of EoE are more marked in the proximal than in the distal esophageal mucosa.

- Differential

- Give the differentiated diagnosis of the causes of food impaction / "foreign body" ingestion.
  - Schatzki ring
  - Peptic strictures
  - EoE (eosinophilic esophagitis)
  - Motility disorder of esophagus
  - Ideopathic

- Endoscopy

- Give 5 changes on EGD in the patient with eosinophilic esophagitis (EE).
  - Corrugation (multiple rings)
  - Longitudinal furrows
  - Mucosa: featureless, fragile (crepe paper)

- White surface vesicles (eosinophilic microabscess)
- Proximal or mid-esophageal stenosis/stricture (may be multiple)
- Small caliber esophagus
- Food impaction
- Note
  - EGD may be normal

Abbreviations: EE, eosinophilic esophagitis; EGD, esophagogastroduodenoscopy

➢ Treatment

- A 30 year old patient with solid food dysphagia presents for an upper endoscopy. There is no history of heartburn or regurgitation, and no family history of esophageal disease. A benign appearing stricture is seen. You suspect eosinophilic esophagitis (EoE). Give the steps in management.

  - Exclude eosinophilic esophagitis (EoE) by biopsy of distal and mid esophagus, >15 eosinophils/hpf
  - If positive for EE, treat for 4 weeks with PPI po od, before specific Rx for EoE (medications and/or dietary therapy).
  - Do not do initial empiric dilation of stricture until EoE disproven, or proven by biopsy and treated
  - Dilate gently and progressively only after treatment of EoE
  - Use generous sedation
  - If perforation occurs, try to avoid surgery, since than esophageal wall does not hold sutures well; may need to do esophagectomy

Abbreviation: EoE, eosinophilic esophagitis

➢ Complications

- Eosinophilic esophagitis is a high risk disease. Give 4 complications.

  - Dysphagia
  - Food impaction
  - Stricture

- Sloughing of mucosa (mucosal eosinophils)
- Mucosal tear
- Perforation
  - EGD
  - Spontaneous (Boerhaave syndrome) from transmural inflammation of EoE

Abbreviation: EGD, esophagogastroduodenoscopy

- Endpoints "improvements in clinical symptoms and esophageal eosinophilic inflammation … symptoms cannot be used alone as a reliable determinant of disease activity and response to therapy….."

- Give the advantages and disadvantages of current medical and nutritional treatment strategies for eosinophilic esophagitis

Treatment	Advantages	Disadvantages
○ Oral steroids (1-2 mg/kg/day: maximum 60 mg)	- Rapid relief of symptoms	• Significant systemic side effects • Prompt recurrence when discontinued
○ Swallowed fluticasone (children 440-880 µg/day; adolescents/adults, 880-1769 µg/day)	- Minimal systemic steroid absorption - Shown to relieve symptoms - Normalizes esophageal mucosa	• Risk of candidal esophagitis • Small amount systemically absorbed • Long term efficacy unknown, but prompt recurrence when discontinued • Difficult for small children and developmentally delayed patients to swallow
○ Viscous budesonide (<10 y, 1 mg daily; >10 y, 2 mg daily)	- Easier to swallow - Theoretically can reach more distal areas of esophagus - Shown to reduce symptoms and normalize esophageal mucosa	• Cumbersome to mix • Theoretical risk of candidal esophagitis • Long term efficacy unknown

Treatment	Advantages	Disadvantages
○ Montelukast (20-40 mg daily)	- Symptomatic relief has been shown at high doses (100mg) - No significant adverse effects	• Not clear whether it improve esophageal eosinophilia • Inadequate studies
○ Cromolyn sodium (100 mg 4 times a day)	- No significant adverse effects	• Inadequate studies
○ Mepolizumab	- Phase II trials in adults show that it is safe - Promising preliminary data in pediatric studies	• Did not induce significant histologic remission in adult study
○ Elemental diet	- 92%-98% effective - Resolution of symptoms in 7-10 days - Histologic remission within 4-5 weeks	• Poor palatability • Usually requires nasogastric or gastrostomy tube • Very expensive • Socially isolating

➢ Elimination diet ("six-food") wheat, milk, soy, eggs, nut, fish/ shellfish

Printed with permission: Hait et al. *Clin Gastroenterol Hepatol* 2009;7:721-4.

➢ Corticosteroids

- ○ Tablets, 20-40 mg prednisone po for 4-6 weeks, followed by slow taper. Indicated in EE persons with acute dysphagia, high risk for esophageal perforation while undergoing repeated dilations, severe weight loss, or refractory to other symptoms.
- ○ Swallowed fluticasone, 1-2 puffs qid for 6-8 weeks for short-term therapy, but not for maintenance
- ○ 70% recurrence rate after initial steroid use, and esophageal dilations may still be necessary.

- Topical steroids for 8 week, with longer cause or higher doses, or systemic steroids in patients without initial symptomatic or histological improvement
- Adult daily doses, in a divided dose
  - Fluticasone 880 to 1760 mcg
  - Budesonide 2 mg
  - Multi-dose inhaler with proper instructions to puff into the mouth during breath hold, then to swallow 2 mg in 4 mL budesonide liquid mixed with 10 gm sucralfate
- Maintenance therapy with topical steroids and / or dietary therapy may be required for
  - Stricture
  - Food impaction
  - Sever dysphagia
  - Rapidly recurring
    - Symptoms, or
    - Histologic relapse

Source: Dellon et al., Amer J Gastro 2013; 108: 679-692.

- Montelukast (leukotriene D4 receptor inhibitor)
  - Not recommended because of lack of reduction of eosinophilic infiltration in the esophageal mucosa.

- Meplizumab (humanized monoclonal IgG antibody to IL-5)
  - Poor response in placebo-controlled study

Adapted from: Bohm M, Richter JE. *Am J Gastroenterol* 2008:1-10.

- PPI plus dilations
  - Symptoms, endoscopic and histology changes may improve
  - Fever dilations required
  - Dilation
    - Associated perforations are mild (pneumomediastinum)
  - It is being shown that it is safe to dilate carefully (45 F) the esophagus after mucosal biopsies have been taken.
  - Persons with EoE and symptomatic strictures despite pharmacologic / dietary therapy may be carefully dilated after the patient being informed of the risks of esophageal dilation in EoE, including "… post-dilation chest pain, which occurs in up to 75% of patients, bleeding, and esophageal perforation"

INFECTIOUS ESOPHAGITIS

Infection's esophagitis often causes odynophagia when an immune-suppressed patient has odynophagia, but the stem of MCQ states that the examination of the mouth is normal → think candidiasis, CMV or HSV infection in the esophagus, even though there are no signs of infection in the mouth.

- Give 3 causes of **infectious esophagitis**, and for each give the recommended antimicrobial therapy
    - Candida Albicans
        - Fluconazole or itraconazole
    - CMV
        - IV ganciclovir foscarnet
    - HSV
        - Oral acyclovir or famciclovir

- Give 5 fungal causes of esophagitis.
    - Candida albicans
    - Aspergillosis
    - Blastomycosis
    - Cryptococcosis
    - Histoplasmosis

Candidiasis

- Etiology
    - Type and Candida albicans infection
        - Candidemia
        - Disseminate candidiasis
        - Focal organ involvement
        - Hepatosplenic (chronic disseminated)
    - Risk factors
        - Oropharyngeal candidiasis
        - HIV-infection, CD4 < 100 cells / µL
        - Drugs
            - Antibiotics, broad spectrum
            - Inhaled corticosteroids
            - Chemotherapy
            - Immunosuppressives

- Catheters
  - TPN
  - Hemodialysis
- Hospitalizations
- Pancreatitis
- Malignancy
- Transplantation
- Recent surgery
- AKI (acute kidney injury)
- Neutropenia

- Clinical: micro-abscesses may be in virtually any organ but especially
  - Eye – White exudates
  - Skin – Painless papules / pustules on red base
  - MSK – Bone; – Joints
  - GI – Peritoneum
  - GU – UTI (urinary tract infection)

- Diagnosis
  - Culture
    - Blood culture is the "gold standard"
    - Negative blood culture does not exclude systemic candidiasis
    - Positive culture from any normally sterile area
    - "Candidiasis species that is obtained from a blood culture should never be considered a contaminant but instead should initiate investigation for a course" (MKSAP 16, Infectious disease 2012, page 39).
  - Tissue biopsy from skin lesion, or any involved organ

  Note: Since candida pneumonia is very rare, sputum culture if usually not done

- Treatment

Note: Treatment is different (please see later) if there is associated systemic/ invasive candidiasis

- Progression of drug classes, depending upon-response
  - Azoles → echinocandins → amphotericin B
  - Candidiasis during pregnancy → amphotericin B

- Azoles
  - Overview
    - Hepatotoxic
    - Teratogenic in pregnancy
    - All azoles are equally effective
    - Multiple drug interactions (CYP450)
    - ↑ risk of drug resistance
  - Nystatin (local)
    - Nystatin swish- and swallow- 400,000 to 600,000 units po qid for 7 to 14 days only for mild disease; clotrimazole or fluconazole higher relapse rate
    - Cotrimazole: one 10 mg trouche dissolved slowly, taken po 5 times a day
    - May be first-time Rx when risk factors (e.g. steroids, chemotherapy) continue and there is no / poor response to nystatin
  - Fluconazole (systemic)
    - Secondary prophylaxis, 100 mg to 200 mg per week, for
    - Restoration of CD4 counts > 100 cells / μL helps to ↓ risk of recurrent candidiasis
    - Recurrent disease, moderate-to-severe infection, or CD4 < 100 cells / μL (at risk for esophageal candidiasis)
    - Risk of cryptococcosis
    - No immune reconstitution on HAART Rx – frequent / severe candidiasis
    - Dosing
      - 200 mg loading dose IV, followed by 100 mg to 200 mg a day for 7 to 14 days
      - Prophylaxis: 100 mg po od
      - HAART therapy to restore CD4 levels > 100 cell/μL to ↓ risk of recurrent C.albicans infection
  - Note: there may be discordance rates in clinical vs. mycological "cure" in cancer patients given cytotoxic Rx

Drug	Clinical cure	Mycological cure
- Fluconazole	74% to 90%	80%
- Itraconazole	62%	68%

  - Itraconazole oral solution
    - 10 mg/mL, 200 mg daily for 7 to 14 days
    - Nausea in > 10%

- Posaconazole
  - 200 mg bid
  - Transient visual disturbance in 23%

- Echinocandins all are given IV for esophageal candidiasis refractory to azoles
  - Caspofungin – 50 mg IV per day for 7 to 21 days
  - Micafungin – 100 mg to 150 mg IV per day
  - Anidulafunfin – 100 mg IV per day

- Amphotericin B
  - Indications
    - Treatment of candidiasis during pregnancy (note: azoles are teratogenic)
    - Resistance to azoles or echinocandins
  - Dosage
    - 0.3 to 0.7 mg/kg per day

Clinical Gems and Pearls

- The presence of oropharyngeal candidiasis may ↑ risk of esophageal infection, but Candida esophagitis may occur even in the absence of oropharyngeal disease.
- An immunosuppressant patient who develops odynophagia / dysphagia, with or without oropharyngeal candidiasis, may be treated empirically with fluconazole
- If a 3 day course of fluconazole does not relieve the esophageal symptoms, perform EGD to determine
  - Other causes of esophagitis, e.g.
    - Pill esophagitis
    - HSV
    - GERD
  - Fluconazole-resistant strains
- When esophageal candidiasis is associated with HIV-seropositivity with CD4 < 100 cells / μL mention HAART therapy to restore CD4 levels to ↓ risk of recurrent C. albicans infection.

- Give the influence of CD4 count on treatment choice for esophageal candidiasis.
  - Risk factors for oropharyngeal candidiasis
    - CD < 200 cells / μL
    - Prior colonization or infection with C. albicans
  - First infection, mild infection, or CD4 > 100 cells /μL
    - Oral nystatin, or clotrimazole trouches po
    - Fluconazole po 200 mg
    - 97% favourable response with 200 mg loading dose followed by 100 mg to 200 mg a day for 7 to 10 days

➢ Special considerations
  - Non-neutropenic
    - Fluconazole
      - First choice for C. parapsilosis
      - If no / poor response, switch to
    - Echinocandin
      - Caspofungin
      - Anidulafungin
      - Micafungin
      - If echinocandin used first for empiric therapy and response is poor, may switch to Fluconazole if patient is stable
      - First choice empiric therapy for Candida glabrata
    - If echinocandin fails when used for C. glabrata, perform susceptibility testing before using
      - Fluconazole, or step-down
      - Voriconazole
    - Treat for 2 weeks after
      - Loss of symptoms
      - Clearance of fungemia
    - Remove possibly causative catheters, central lines
  - HIV-seronegative: oral

Note discordance rates in clinical vs. mycological “cure” in cancer patients given cytotoxic Rx

Drug	Clinical cure	Mycological cure
- Fluconazole	74% to 90%	80%
- Itraconazole	62%	68%

- Neutropenic
  - Echinocandin, or
  - Voriconazole, or
  - Amphotericin B, echinocandin, or
  - Voriconazole
- Immunocompromised
  - Symptom relief: viscous xylocaine / lidocaine, gargle / swallow ~ 300 mg/dose, ≤ 8x / day
  - For severe disease (odynophagia, dysphagia, or unable to swallow):
    - Acyclovir 5 mg/kg IV q 8 h for 7 to 14 days
    - Acyclovir-resistant (cross-resistance of valacyclovir and famcyclovir to mutations of thymidine kinase or DNA polymerase): use foscarnet
- Asymptomatic cystitis
  - Treat with fluconazole, if patient
    - Neutropenic
    - Having urologic surgery
- Focal infections
  - Meningitis
  - Endophthalmitis

Note: Do <u>not</u> use echinocandins

- HIV-seropositive
  - HAART therapy
    - Restoration of CD4 counts > 100 cells / μL helps to ↓ risk of recurrent disease
    - Recurrent disease, moderate-to-severe infection, or CD4 < 100 cells / μL (at risk for esophageal candidiasis)
      - Fluconazole po 200 mg loading dose, followed by 100 mg to 200 mg a day for 7 to 14 days.
  - Risk factors for oropharyngeal candidiasis
    - CD4 < 200 cells / μL
    - Prior colonization or infection with C. albicans
  - First infection, mild infection or CD4 > 100 cells /μL
    - Oral nystatin or clotrimazole trouches
    - Fluconazole po 200 mg
    - 97% favourable response loading dose, followed by 100 mg to 200 mg a day

- Systemic / Invasion Candidiasis
  - Candidemia
  - Disseminate candidiasis
  - Focal organ involvement
  - Hepatosplenic (chronic disseminated)

Herpes Simplex Virus (HSV) esophagitis

- Usually HSV type-1 rather HSV than type-2
- Source of infection
  - Oropharyngeal HSV, extending directly into esophagus
  - Reactivation with indirect spread of HSV along vagus nerve into esophagus
  - HSV esophagitis may occur together with CMV infection

- Associations
  - Immunosuppression (may also occur in immunocompetent persons)
    - Transplantation setting
    - During acute rejection

ESOPHAGEAL MOTILITY DISORDERS

- Definition: A patient is said to have an esophageal motility disorder if their findings on motility study are two standard deviations beyond normal.

- Types
  - Esophageal motility disorders may be primary, or secondary to (associated with) another disease process.

- Manometry
  - Testing conditions for ambulatory manometry are less well standardized as compared with stationary manometry.
  - HRM (high resolution manometry) allows for topographic plotting of esophageal pressures in a test called HREPT (high-resolution esophageal pressure topography).

- Give advantages of high-resolution manometry (HRM) in the management of achalasia allows for better definition of esophageal motility disorders, including achalasia.
    - Achalasia classified into three subtypes: type I (classic achalasia), type II (esophageal compression), and type III (spastic achalasia).
    - Response to achalasia treatment appears to vary by subtypes.
    - There is some variability in distinguishing between type I and type II achalasia.
    - Thus, clarification of the criteria for type I and type II achalasia might improve the reliability of the classification.

Source: Hernandez et al. Am J Gastroenterol 2012; 107:

- Esophageal intraluminal pH testing is now being incorporated into EMIIT (esophageal multichannel intraluminal impedence testing).
- Normal: Normal velocity, < 8 cm/s in > 90% of swallows; normal peristaltic amplitude; (≥7 peristaltic contractions with an intact wave progression, amplitude >30 mmHg)
- Aperistalsis: Absent or simultaneous contractions (<30 mmHg)
- Ineffective esophageal motility (IEM): ≥3 peristaltic contractions with failure of wave progression due to
    - An ineffective distal contraction amplitude (<30 mmHg) or
    - Failed peristalsis over a segment of the distal esophagus
- Isolated hypertensive LES: basal LES pressure greater than 45 mmHg (mid-respiratory pressure)
- Achalasia: abnormal LES relaxation; absent or simultaneous contractions (no primary peristalsis waves)
- Atypical disorders of LES relaxation: abnormal LES relaxation, with some normal, may have simultaneous or absent peristalsis.
- One peristaltic contraction rules out achalasia (Katz 09). The motility changes of achalasia include
    - ↑ LES pressure
    - ↑ residual pressure of LES (incomplete relaxation)
    - Complete absence of peristalsis
- In DES (distal or diffuse esophageal spasm), there is an uncertain relationship between symptoms and the DES motility changes
- The nutcracker esophagus and a hypertensive LES may be seen in persons with GERD

- A video barium examination may be normal even when UES manometry is abnormal
- It is useful to perform provocative testing (intraesophageal acid infusion, balloon distention, edrophonium injection) to attempt to reproduce the patient's symptoms in the setting of NCCP (non cardiac chest pain)
- Combined multichannel intraluminal impedence (MII) and pH testing detects impedence data at 3, 5, 7, 9 and 15 and 17 cm above the LES, and 5 cm above the LES

Abbreviations: DES, distal or diffuse esophageal spasm; DSRS, distal splenorenal shunt; EHT, endoscopic hemostatic therapy; LES, lower esophageal sphincter; MCTD, mixed connective tissue diseases; MII, multichannel intraluminal impedence; TIPS, transjugular intrahepatic postoperative shunt; tLESR, transient lower esophageal sphincter relaxation

Printed with permission: Sifrim D and Fornari F. *Best Pract Res Clin Gastroenterol* 2007;21(4): pg. 575-576.

- Classify esophageal motor abnormalities, and give the qualitative changes in motility in the upper esophageal sphincter (UES), esophageal body (EB) and lower esophageal sphincter (LES) of 4 conventional manometric (dysmotility) syndromes.

Upper esophageal sphincter	Esophageal body (EB)	LES
➢ ↑ Contraction ○ Zenker diverticulum	↑ Contraction – Nutcracker esophagus – Achalasia (compartmentalized pressurization)	↑ Pressure ▪ Isolated hypertensive LES ▪ Achalasia
➢ ↓ Contraction ○ MCTD (e.g. scleroderma) ○ Oculopharyngeal dystrophy	↓ Contraction* – Ineffective esophageal motility (IEM) – Aperistalsis (e.g. scleroderma)	↓ Pressure ▪ Hypotensive LES ▪ GERD (↑ tLESR) ▪ Scleroderma
➢ ↓ Co-ordination ○ Achalasia (complicated) ○ Parkinson disease ○ Cricopharyngeal bar ○ Belch dysfunction	↓ Co-ordination – Diffuse esophageal spasm (DES) – Achalasia (absent or simultaneous contractions)	↓ Co-ordination ▪ (relaxation**) ▪ Achalasia, type I ▪ Atypical LES relaxation ▪ Post-fundoplication gas-bloat syndrome

* contraction, or impaired retrograde inhibition

** relaxation, or inadequate swallow-induced inhibition

- **Classification** of esophageal motility disorders (EMD)

Primary EMD	Second EMD	Manometric variants
○ Achalasia (three subtypes)	– Pseudoachalasia	▪ Hypertensive peristalsis
○ Diffuse esophageal spasm	– Chagas disease	▪ Hypertensive LES
○ Nutcracker	– Scleroderma esophagus	▪ Ineffective esophageal motility
○ Absent peristalsis	– Parkinson disease	
○ Gastroesophageal reflux disease (GERD)	– Infiltrative disorders	

- Spastic esophageal motility disorders
  - DES (diffuse [or distal] esophageal spasm
  - Nutcracker and spastic esophagus
    - Nutcracker esophagus may be a hypercholinergic condition which leads to a loss of the normal synchrony between the inner circular and other longitudinal smooth muscle layers of the esophagus.
    - Modest ↑ amplitude → dysphagia plus NCCP (non-cardiac chest pain)
    - ≥ 20% simultaneous contractions with an amplitude of > 30 mm Hg
    - 1/3 of DES patients also have ↑ LES pressure and ↓ LES relaxation
    - This latter subgroup of DES may actually have achalasia (on HREPT, distal latency plus DES may be spastic achalasia).
    - Barium swallow in DES
      - May be normal, or show corkscrew esophagus
      - Low sensitivity and specificity
    - The average amplitude in the distal 10 cm of esophagus from ≥ 10 5 mL liquid swallows, ≥ 220 mm Hg
    - HREPT defines 2 subgroups of nutcracker esophagus, based on the DCI (distal contractile integral)
    - DCI is an integration of the amplitude, duration and length duration of a contraction.
    - DCI is expressed as mm Hg.s.cm

- Values of DCI on HREPT
  - Normal ≤ 5000 mm Hg.s.cm
  - Nutcracker 5000 to 8000 mm.Hg.s.cm
  - Spastic nutcracker 8000 mm.Hg.s.cm
- May be associated with ↑ LESP pressure and ↓ LES relaxation.
- The manometric diagnosis of a motility disorder may change if it is performed at a time the patient is having symptoms.

- Hypertensive LES (lower esophageal sphincter)
  - Resting LES > 45 mm Hg
  - ~ 50% have ↓ LES (> 35 mm Hg on HREPT) relaxation and ↑ amplitude distal esophageal contraction amplitude (as high as ≥ 220 mm Hg).
  - The relationship between a manometric event and the patient's symptoms may be poor, and association indices have been developed to establish the probability of a cause and effect relationship between a motility event, e.g. gastroesophageal reflux or DES, and patient symptoms, e.g. heartburn or NCCP (non-cardiac chest pain).

➢ High resolution manometry

- Give the advantages of high resolution esophageal manometry (HREM), and high resolution esophageal pressure topography (HREPT) include:
  - High quality, uniform format
  - Greater reproducibility
  - Viewing simultaneous contractions of the entire esophagus
  - Standardized objective metrics
  - Topographic patterns easily learned and recognized
  - Allows for subclassification of achalasia, and of DES.

Useful background: Esophageal motor abnormalities based on high-resolution manometry.

Diagnostic criteria for esophageal motility

- Normal
  - Normal EGJ pressure (10-35 mm Hg) and relaxation (see below)
  - Peristaltic velocity <8 cm/s in >90% of swallows
  - Normal elevation of intra-bolus pressure at <8 cm/s to <30 mm Hg in > 90% of swallows
  - Mean distal contractile index (DCI) <5000 mm Hg·s·cm**
- Peristaltic dysfunction
  - Mild: 3-6 swallows with failed peristalsis or a >2 cm defect in the 30 mm Hg isobaric contour of the distal esophageal peristalsis (15 mm Hg in proximal-mid esophagus)
  - Severe: ≥ 7 swallows with either failed peristalsis or a >2 cm defect in the 30 mm Hg isobaric contour of distal esophageal peristalsis (15 mm Hg in proximal-mid esophagus)
  - Aperistalsis: Contractile pressure <30 mm Hg throughout mid-distal esophagus in all swallows (*Scleroderma* pattern: aperistalsis with LES pressure <10 mm Hg)
- Hypertensive dysfunction
  - Peristaltic velocity <8 cm/s in >80% of swallows
  - Mean distal contractile index (DCI) >5000 mm Hg·s·cm**
    - *Hypertensive peristalsis*: mean DCI >5000-8000 mm Hg·s·cm
    - *Segmental hypertensive peristalsis*: hypertensive contraction restricted to mid- or distal esophagus or LOS after-contraction: mean DCI 5000-8000 mm Hg·s·cm
    - Hypertensive peristalsis ± repetitive or prolonged contraction: DCI >8000 mm Hg·s·cm
- Esophageal spasm (rapidly propagated contractile wavefront)
  - Peristaltic velocity >8cm/s in ≥20% of swallows ± raised DCI
    - *Diffuse esophageal spasm:* rapid contractile wavefront throughout the distal esophagus
    - *Segmental esophageal spasm*: rapid contractile wavefront limited to mid or distal esophageal segment

- Rapid elevation of intra-bolus pressure *(*increased resistance to flow due to functional or structural obstruction in the esophagus or at the esophago-gastric junction [e.g. stricture, post-fundoplication, eosinophilic esophagitis, poorly coordinated contractions])
  - Rapid elevation of intra-bolus pressure to >15 mm Hg in >8 cm/s in ≥20% of swallows
    - Mild: Intra-esophageal bolus pressure (15 to 30 mm Hg) with ≥80% preserved peristalsis
    - *Severe*: Intra-esophageal bolus pressure (>30 mm Hg) with ≥20% failed peristalsis

➢ Treatment

- Non-immunocompromised
  - Spontaneous remission is usual before 2 weeks;
  - Acyclovir 200 mg po 5x / day, or 400 mg po tid for 7 to 14 days for faster symptom relief
- Immunocompromised
  - Symptom relief: viscous xylocaine / lidocaine, gargle / swallow ~ 300 mg/dose, ≤ 8x / day
  - For severe disease (odynophagia, dysphagia, or unable to swallow):
    - Acyclovir 5 mg/kg IV q 8 h for 7 to 14 days
    - Acyclovir-resistant (cross-resistance of valacyclovir and famcyclovir to mutations of thymidine kinase or DNA polymerase): use foscarnet

- Give the **treatment** of DES, nutcracker esophagus and hypertensive LES (spastic esophageal motility disorders)
  - Generally small, less than ideal studies
  - Peppermint oil po prn
  - Warm / hot water
  - Botulinum toxin endoscopic injection
    - 20 units / mL injection at the Z-line 5 circumferential injections
    - Inhibits the acetylcholine-releasing excitatory neurons innervating the smooth muscle of the LES, which thereby lowers the LES pressure.
  - Management of any associated psychological symptoms

- Calcium channel blocker
  - Diltiazem 60 mg to 90 mg po qid
- Anti-depressant
  - Trazodone 100 mg to 150 mg/day
  - Imipramine 50 mg/day at bedtime
- Anticholinergic
  - Bethanechol
- Anti-phosphodiesterase
  - Sildenafil (50 mg prn); tadalafil; vardenafil
- Nitrates
  - Isosorbide 10 mg
- Pneumatic dilation
- Surgical myotomy

ZENKER DIVERTICULUM (ZD)

- Definition
  - A protrusion of the mucosa of the upper esophagus through Killian's triangle (oblique muscle of the inferior pharyngeal constrictor muscle and the cricopharyngeal sphincter) to produce a false diverticulum ("pseudodiverticulum") with its neck proximal to the cricopharyngeal muscle.

- Pathogenesis
  - Motor abnormalities of upper esophagus
    - ↑ degeneration of muscle fibres in upper esophagus
    - ↑ replacement of degenerated muscle with fibrous and adipose tissue
    - ↑ hiatus hernia (possibly from ↑ GER)
    - ↓ opening of UES (upper esophageal sphincter)
    - ↑ intrabolus pressure upon swallowing
    - ↑ GER (gastroesophageal reflux > 50%, BE [Barrett epithelium] in ~20%)
  - ↑ risk of squamous cell carcinoma in the diverticulum

- Treatment
  - Medical
    - PPI for symptoms of GERD
    - Endoscopic
  - Endoscopic (flexible) or surgical (internal) myotomy of crycopharyngeal muscle (sphincterotomy) with diverticulopexy
    - ESED (endoscopic stapler esophagodiverticulostomy)
    - Endoscopic surveillance for BE in presence of GERD symptoms (controversial)
    - Early EGD for dysphagia (↑ risk of squamous and adenocarcinoma)
  - Surgical
    - One-or-two-step surgical excision of ZD
    - External sphincterotomy

ACHALASIA

- Definition
  - In order to make the diagnosis of achalasia, there must be standard manometric or HREPT evidence of
    - Loss of relaxation of LES (lower esophageal sphincter), plus
    - Loss of peristalsis in distal esophagus
    - ↑ LES pressure (↓ variable)

- Primary achalasia
  - Primary achalasia is associated with unexplained loss of ganglion cells in the myenteric plexus of the esophagus.
  - Relaxation and/or opening in swallowing
  - ↑ intra-esophageal bolus pressure due to resistance to flow at EGJ
    - *Classic*: aperistalsis with no identifiable contractile activity
    - *Vigorous*: with persistent contractile activity (spasm) or gross elevation of intra-esophageal bolus pressure, with or without esophageal shortening
    - *Variant*: with preserved peristalsis in the distal esophagus in ≥20% swallows

- Classify the 3 types of achalasia made by high-resolution manometry, and compare the treatment responses with each type.

	Type I	Type II	Type III
➢ Peristalsis			
○ Absent peristalsis	+		
○ Compartmentalized pressurization		+	
○ Spastic contraction			+
➢ Response to treatment			
○ Heller myotomy	67	100%	0
○ Pneumatic dilation	38	73%	9
○ Botulinim toxin	0	86%	22

Printed with permission: Pandolfino et al. *Gastroenterology* 2008;135: pg. 1526-33.

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Achalasia is rare, and an even rarer condition is achalasia secondary to a tumor (e.g. small cell lung cancer).

- Give the molecular basis for the paraneoplastic syndrome which may case secondary achalasia, gastroparesis, small intestinal pseudo-obstruction, or colonic intertia.
  - An epitope on the cancer forms an antibody (anti-Hu) which attaches to the myenteric plexus of different portions of the GI tract, resulting in dysmotility.

- Give 15 causes of secondary (pseudoachalasia) achalasia.
  - Infection/Infiltration
    - Sarcoidosis
    - Sjogren syndrome
    - Amyloidosis
    - Fabry disease
    - Chagas disease (Trypanosoma cruzi)

- Cancer (GI)
  - Squamous cell carcinoma of the esophagus
  - Adenocarcinoma of the esophagus
  - Hepatocellular carcinoma
  - Pancreatic adenocarcinoma
- Cancer (Non-GI; Paraneoplastic syndrome)
  - Lung carcinoma (non-small cell)
  - Breast adenocarcinoma
  - Metastatic renal cell carcinoma
  - Metastatic prostate carcinoma
  - Leiomyoma
  - Lymphoma
  - Reticulum cell sarcoma
  - Lymphangioma
  - Mesothelioma
- Motility
  - Parkinson disease
  - Achalasia with associated Hirchsprung disease
  - Hereditary hollow visceral myopathy
  - Familial achalasia
  - Fundoplication
- Surgery
  - Post-fundoplication
  - Post-vagotomy
- Miscellaneous
  - Allgrove (AAA) syndrome – (Alacidygia; Addisons; Achalasia)
  - Hereditary cerebellar ataxia
  - Autoimmune polyglandular syndrome type II
  - MEN IIb (Sipple Syndrome)

Adapted from: Clouse RE, et al. *Sleisenger & Fordtran's gastrointestinal and liver disease: Pathophysiology/Diagnosis/Management* 2006:871.

➢ Treatment

- Pharmaceutical
  - Smooth muscle relaxation (relaxants taken 15 to 30 min before meals)
    - Nitrates
    - Calcium channel blockers
      - Nifedipine 60 mg to 90 mg po qid
    - Use same doses as for spastic esophageal motility disorders
    - Botulinum toxin injection into the area of LES
      - Inhibits the acetylcholine-releasing excitatory neurons innervating the smooth muscle of the LES (lower esophageal sphincter), which thereby lowers the LES pressure.
  - Smooth muscle damage
    - Esophageal dilation
      - Bougie
      - Forceful balloon dilation (tears some of the smooth muscle fibres)
      - Success rates

Months	%
6	74%
12	68 to 90%
24	86%
≥ 36	58%

      - Post-procedure
      - Perforation 2 to 4%
      - Heartburn 45%
      - May require repeated dilations if dilation approaches fail, there may be risk of complications from subsequent surgical myotomy
        - Especially if patient < 40 years
        - 25% to 50% within 5 years

- Endoscopic
- Give the influence (approximate %) of endoscopic procedures performed for achalasia (pneumatic dilation or injection of botulinum toxin) which fail, and are followed by surgical myotomy, as compared with surgical myotomy not proceed by endoscopic treatment.

Adverse outcomes	Surgical myotomy alone	Surgical myotomy preceeded by endoscopic therapy
○ Complications		
– Intraoperative	4%	10%
– Post-operative	5%	10%
○ Persistent or recurrent symptoms	10%	20%

  - Perforation
    - 2 - 4%
  - Heartburn
    - 45%
  - May require repeated dilations
  - ↑ risk of complications from subsequent surgical myotomy
    - Especially if patient < 40 years
    - 25% to 50% within 5 years

- Surgical myotomy (Heller myotomy)
  - Open (thoracic, or abdominal approach)
    - Success rate higher (70% to 90%), and recurrence rate 10 years, 70% to 85%; 20-30 years, 65% to 75% lower than forceful pneumatic dilation
    - Longterm complications include
      - GER (gastroesophageal reflux) (heartburn, strictures, BE and adenocarcinoma of esophagus)
      - With fundoplication, risk of GER falls from 32% to 9%
    - Short-term complications
      - Esophageal perforation ~5%
      - Mortality < 1 / 10^3

The 5 year likelihood of being asymptomatic after laparoscopic myotomy for achalasia is 87%.

- Give the preoperative factors which are associated with a higher risk of failure from laparoscopic myotomy.
  - LES pressure > 30 mm Hg (high)
  - Dilated S (sigmoid) shaped esophagus
  - NCCP (non-cardiac chest pain)
  - Endoscopy (POEM, PerOral Endoscopic Myotomy [a form of NOTES: Natural Orifice Transluminal Endoscopic Surgery])
    - Peroral endoscopic myotomy (POEM) has been demonstrated to be a highly effective treatment resulting in a more than 90% clinical success rate, improved Eckhard symptom score, as well as improved manometry outcomes.

Source: von Rentein D, et al. Am J Gastroenterol 2012; 107: 411-417.

SCLERODERMA ESOPHAGUS

Scleroderma (systemic sclerosis [SSc] is associated with involvement of several parts of the GI tract, leading to dysfunction and symptoms

- Give the effect of scleroderma on the GI tract, and outline the treatment for 5 examples.
  - Mouth xerostomia
    - Facial exercises (small mouth)
    - Artificial hygiene
    - Artificial saliva
  - Esophagus
    - SSc associated loss of LES and peristalsis leads to ↑ risk of GERD symtoms and esophagitis, including severe (LA C-D) disease
    - Treat the GERD as per usual (non-SSc), remembering the higher risk of:
      - Need for higher dose PPI
      - NAB (nocturnal acid breakthrough)
      - Strictures
      - ENT complications, especially aspiration
      - Pill-associated esophagitis

- Stomach
  - Delayed gastric emptying (may worsen GERD)
  - Bleeding from telangiectasia
- Small intestine
  - Small intestinal bacterial overgrowth (SIBO)
    - Slow small intestinal transit in SSc from ↓ MMCs (migrating motor complexes) → SIBO
    - Treat associated disorders plus nutrient deficiencies
    - Antibiotic therapy (7 to 10 days); then intermittent, episodic, continuous, or rotational
      - Tetracycline 250 mg po qid
      - Trimethrim 200 mg po bid
      - Amoxicillin-clavulanate po tid
      - Metronidazole 250 mg to 500 mg tid to qid
    - Probiotics (weak evidence for beneficial maintenance therapy)
  - Dysmotility, pseudo-obstruction, nutritional risk
    - Octreotide injection
    - TPN (total parenteral nutrition)
    - HPN (home parenteral nutrition)
    - PE / PEJ (percutaneous endoscopically-placed gastrostomy or jejunostomy feeding tube)
  - Pneumatosis cystoides intestinalis, pneumoperitoneum
    - ↓ dietary intake of gas-forming malabsorbed carbohydrates
    - Antibiotics (SIBO)
    - O_2 therapy
    - Hyperbaric O_2
- Colon
  - Constipation
  - Fecal incontinence
  - Wide-mouthed colonic diverticula
- Liver
  - PBC (primary biliary cirrhosis)

ESOPHAGEAL VARICEAL BLEEDING

➢ Anatomy

- Give the 4 zones of venous drainage in EV.
  - Truncal zone
    - 10 cm in length, above perforating zone
    - 4 longitudinal veins in the lamina propria
  - Perforating zone
    - Above palsade zone
    - Network of esophageal submucosal veins anastomose with periesophageal external veins
    - Periesophageal veins drain into azygous system
  - Palisade zone
    - 2-3 cm above GE junction
    - 4 longitudinal veins anastomose with veins in the lamina propria
    - No anastomosis with periesophageal external (i.e., no perforating veins) veins
    - Limited soft tissue support high risk of bleeding
  - Gastric zone
    - 2-3 cm below GE junctions
    - Longitudinal veins in submucosal and lamina propria these longituding veins gather at the gastric cardia and drain into short gastric and left gastric veins

➢ Pathogenesis

- Portal vein (PV) pressure is normally 5 to 10 mm Hg
- Cirrhosis → ↓ NO production → ↑ intrahepatic vasoconstriction (reversible) → splanchnic arteriolar vasodilation → ↑ PV (portal vein) blood flow → ↑ PP → hepatic sinusoids become distorted → ↑ resistance to outflow through HV (hepatic vein) → ↑ PP
- HVPG = PV pressure (or WHVP) – HV pressure =

1 to 5 mm Hg	normal
>10 mm Hg	EV develop
> 12 mm Hg	EVB

- The WHVP (wedge hepatic venous pressure) can be obtained from catheterization of HV, as also can the free HV pressure
- WHVP approximates the value of PV pressure, so can be used to estimate HVPG.

Abbreviations: EV, esophageal varices; EVB, esophageal variceal bleeding; NO, nitric oxide

- Give the pathogenesis of EV (esophageal varices).
    - When the pressure (P) in the esophageal varix rises (> 12 mm Hg), when the radius (r) of the varix increases (small → large varices), and when the thickness of the wall of the varix (w) becomes thin because of the enlarging and dilating vein, then according to the law of Laplace (T = Pr/w), the tension (t) on the wall of the varix becomes so great that a hole develops in the ruptured wall of the vein, and profuse bleeding occurs.

➢ Classification of EV
- F1
    - Small, straight
- F2
    - Large, tortuous, fill < 1/3 of lumen
- F3
    - Large, coiled fill > 1/3 of lumen

- Give the **SARIN classification** of gastroesophageal varices (GEV) or isolated gastric varices (IGV).
    - GEV1
        - GV in continuity with EV
        - Extend 2 to 5 cm below GE junction
        - Easiest to obliterate with cyanoacrylate
    - GEV2
        - GV in continuity with EV
        - GV extend to cardia and fundus
    - IGV1
        - No EV
        - GV in fundus
        - Most difficult to obliterate with cyanoacrylate
    - IGV2
        - No EV
        - GV in gastric body, antrum, and pylorus
    - Bleeding risk
        - GEV2 IGV1 > GEV1, IGV2 (unless patient is matched for CTP score, in which case the risk of bleeding is similar for each type of varix)

- Clinical risk
  - Presence of varices at diagnosis of cirrhosis
    - Compensated
      - 30%
    - Decompensated
      - 60%
  - Risk of first EVB 12% per year
  - Risk of death from each EVB ~20%

Clinical Alert

While videofluoroscopy may be a good test to detect a small ZD, video capsule endoscopy is not! Give the reason why?

- The capsule device may become trapped in the pseudodiverticulum.

- Give the factors in a person with liver disease and known esophageal varices which predict a high risk for the first variceal bleeding in the future.

Clinical	- Childs class/ MELD score > 15 - Previous variceal bleed - Alcohol consumption
Endoscopic	- Large esophageal varices - Red colour sign - Presence of gastric or proximal esophageal varices - Presence of portal hypertensive gastropathy
Hemodynamic	- Intra-esophageal variceal pressure - ↑ HVPG > 12 mm Hg
Blood tests	- Platelets < 140-150 k - Ratios spleen diameter/platelets - Liver span/albumin
Ultrasound	- Collateral flow on Doppler ultrasound - Flow reversal in potential vein (PV) - Congestion index of the portal vein - Portal vein size > 10-13 mm

Adapted from: Franchis de, R, and Dell'Era A. *Best Pract Res Clin Gastroenterol* 2007; 21(1): 11.

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In persons with portal hypertension from cirrhosis, there is

- Splanchnic arteriolar vasodilation, causing ↑ blood flow in portal vein, and yet there is ↓ blood flow in hepatic vein from hepatic sinusoidal distortion and intrahepatic vasoconstriction.

- Give the rational for giving a NSBB (non-selective beta-blocker) to prevent EVB.

  - The objective is to reduce the WHVP (wedge hepatic venous pressure) to < 12 mm Hg, to prevent EVB
    - ↓ beta-adrenergic vasodilatory tone in mesenteric arterioles → ↑vasoconstriction
    - ↓ portal venous in flow → ↓ portal pressure → ↓ HVPE → ↓ EVB
    - ↑ alpha adrenergic vasoconstriction tone in the vessels → ↑ portohepatic outflow resistance

➢ Treatment

- Screening (in compensated or decompensated cirrhosis)
  - Determine if there are EV (esophageal varices)
  - Pre-primary prophylaxis of development of EV prophylaxis to ↓ risk of development of EV
- Preprimary prophylaxis
  - Before varices develop, to prevent future bleeding
    - Prophylactic treatment not proven
    - Repeat EGD in 2-3 years
- Primary prophylaxis
  - Prevention of first bleed from EV using non-selective beta blocker (NSBB)

    Varices < 5 cm, Child A, B – continue EGD surveillance of size of EV

    Child C – NSBB

    < 5 cm Child B -- NSBB, or EVL
- Secondary prophylaxis
  - Prevent recurrent EVB
- Acute bleeding
  - Stop EVB

➢ Acute bleeding

Risk Stratification-based Therapy for EV

- "clinically significant" PHT = HVPG > 10 mm Hg, or abnormal FibroScan®
- HVPG < 12 mm Hg or ↓ HVPG by > 20% from baseline →
  - ↓ risk of EV bleed
  - ↓ mortality
- For Child class C, 13 to 15 points, consider early TIPS

Abbreviation: TIPS, tranjugular intrahepatic portosystemic shunt; EV, esophageal varices; HVPG, hepatic venous pressure gradient

- Give the diagnosis and management strategy of patients with acute variceal hemorrhage.
  - Diagnosis
    - Any of the following findings on upper endoscopy performed within 12 h of admission:
    - Active bleeding from a varix or stigmata of variceal hemorrhage (white nipple sign) or
    - Presence of gastroesophageal varices without another source of hemorrhage
  - General management
    - Cautious transfusion of fluids and blood products, aiming to maintain a hemoglobin of ~8g/dL
    - Antibiotic prophylaxis (3-7 days) with:
    - Ciprofloxacin 500 mg b.i.d (p.o) or 400 mg b.i.d (i.v), or
    - Ceftriaxone 1g/day (i.v) particularly in facilities with known quinolone resistance and in patients with two or more of the following: malnutrition, ascites, encephalopathy, serum bilirubin >3 mg/dL
  - Specific initial management
    - Pharmacological therapy initiated as soon as diagnosis is suspected; Octreotide 50 mcg i.v bolus, followed by continuous infusion 50 mcg/h (3-5 days), and endoscopic therapy (ligation preferable) performed at time of diagnostic endoscopy (performed within 12 h of admission)

- Rescue management
  - Considered in patients with bleeding esophageal varices who have failed pharmacological and endoscopic therapy or in patients with bleeding gastric fundal varices who have failed one endoscopic therapy
  - TIPS or shunt surgery where available (CTP A patients)

Abbreviations: BID, twice a day; CTP, Child Turcotte Pugh; PO, orally; TIPS, transjugular intrahepatic portosystemic shunt

Printed with permission: Garcia Tsao, et al. Am J Gastroenterol 2009; 104:1808.

- Rebleeding of EV occurs within 1-2 yr in ~ 60% of patients, with mortality of ~ 30%
- ABCs, fluid and electrolytes, including PRBCs to target hemoglobin concentration of 70 g/dL.
- Vasoconstrictor IV for 2-5 days
  - Octreotide bolus (may be repeated once), 50 mcg, followed by IV infusion of 50 mcg / hr
  - Somatostatin bolus (may be repeated once), 250 mcg, followed by IV infusion of 250-500 mcg / hr
  - Terlipressin 2 mg q 4 h for 48 hr, then 1 mg q 4 h for 2-5 days
  - If bleeding recurs after vasoconstrictor and/or EVL, consider transjugular intrahepatic portosystemic shunt (salvage; standard therapy fails in 10% - 20%)
  - Perform at initial diagnostic EGD, band all varices
- TIPS
  - EVL
  - Repeat for rebleeding, or consider tips
  - Note: EV sclerotherapy is used only if EVL is not available
  - Ceftriaxone 1 g IV od for 5-7 days / discharge
  - Norfloxacin 400 mg po bid for 5-7 days / discharge
  - Note
    Continue antibiotic long-term if SBP occurs
    Balloon tamponade is not considered first time therapy

Abbreviation: SBP, spontaneous bacterial peritonitis

Transjugular Intrahepatic Portosystemic Shunt (TIPS)

- Consider early use of TIPS for Child C score of between 10 to 13 points

With the TIPS (transjugular intrahepatic portosystemic stent) a coated stent is inserted between the hepatic vein (HV) and a branch of portal vein (PV) to form the equivalent of a portocaval shunt

- Give 4 accepted indications for TIPS.
  - Varices
    - Bleeding esophageal [EV] or gastric [GV])
    - Preventing rebleeding of EV
  - Ascites, refractory
  - Hepatorenal syndrome
  - BSC (Budd-Chiari syndrome)
  - Hepatic hydrothorax

Notes from **Guidelines on Primary prophylaxis**

- EBL (endoscopic ligation)
  - Perform every 2-4 week until EV obliterated
  - When EV obliterated, repeat EBL q 1-3 mon, then q 6-12 mon indefinitely
- NSBB (non-specific beta blockers)
  - Nadolol 40 mg po od, or propranolol 20 mg po bid, then
  - Increase dose to reduce heart rate ≤ 55 bpm, or
  - Maximal tolerated dose
  - Then EBL for secondary prophylaxis in patient initially treated with EVL for acute EV bleeding
- Risk of first bleed
  - No β-blocker 25%
  - With β-blocker 15%
  - ARR 10%
  - NNT 10

- Mortality rate
  - No β-blocker, 28%
  - With β-blocker, 24%
  - ARR, 4.5%
  - NNT, 22
- Shortcoming of NSBB
  - Always and issue of patient compliance
  - Using HR < 60 or a 25% ↓ HR as an indirect marker for the adequacy of NSBB
    - Only persons with better liver function (~1/3 of total group) respond to NSBB
  - Using HR / ↓ HR is not a good predictor of HVPG
  - When HVPG < 12 mm HG, EV bleeding does still sometimes occur, and bleeding from EV certainly does occur
  - Cautious use in pregnancy, trimesters 2 and 3 (FDAD)
    - Intrauterine growth retardation
    - Fetal bradycardia

Abbreviations: ARR, absolute risk reduction; bpm, beats per minute; EV, esophageal varices; EVL, endoscopic variceal ligation; GV, gastric varices; HR, heart rate; NNT, number need to treat; NSBB, non-specific beta-blocker

- Primary prophylaxis
  - Low risk
    - NSBB (non-selective beta blockers)
      - Small, medium or large EV, plus
      - Red wale marks; or
      - Child B or C cirrhosis
      - Of no use for pre-primary prophylaxis
        - ↓ progression of small to large EV
        - ↓ cumulative probability of EVB
  - High risk
    - NSBB (non-selective beta blockers)
      - ↓ MR (mortality rate) from EVB (5% versus 10% with placebo)
      - ↓ MR (trend) from all causes (21% versus 27% with placebo; or 0.7)
    - EVL (endoscopic variceal ligation)
      - If NSBB fail to prevent enlargement of EV → EVL
      - EVL may be superior primary prophylaxis for large (F2 or F3) varices

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- NSBB reduce the beta adrenergic vasodilatory tone in the mesenteric arterioles, and this reduces portal vein inflow and portal pressure.
- However, NSBB leads to unopposed and therefore ↑ alpha adrenergic vasoconstriction
- The ↑ alpha adrenergic vasoconstriction leads to ↑ portohepatic outflow resistance.
- Thus, the alpha 1 effect partially offsets the beneficial beta effect. Therefore, it may be reasonably postulated that nitrates, which decrease portal pressure, would be beneficial when added to NSBB to reduce the portal pressure and EVB.

- Give the reasons why the combination of nitrates with NSBB is not recommended for primary prophylaxis for EVB.

The combination of nitrates plus NSBB did **not** achieve consistent significance

↓ EVB (NNT ~ 10)

↓ MR from EVB

Abbreviations: EVB, esophageal variceal bleeding; MR, mortality rate; NNT, number needed to treat; NSBB, non-selective beta blocker

➢ Endoscopic variceal ligation (EVL)

Outcome	No EVL, RR
– Risk of first EVB	0.36
– EVB-related mortality	0.20
– All-cause mortality	0.50

- EVL has comparable benefit as NVBB for primary prevention; except
  - Possibly EVL being superior for large EV
  - Cost effectiveness considering
    - QoL (quality of life) EVL > NSBB
    - Life-years gained EVL = NSBB
- After first EBL for primary prophylaxis of EVB, repeat then check for EBL q 2 weeks until all EV are obliterates, then check for recurrence of EV 1 to 3 month later, then q 6 to q 12 months.

- Secondary prophylaxis of EV prevention of rebleeding
  - Risk of rebleeding after first EV bleed
    - 80% at 2 years
  - If Child Pugh score ≥ 7, consider liver transplantation

- Give the first and second line management strategy in the prevention of recurrent variceal hemorrhage (secondary prophylaxis).

First line therapy	- Nonselective ß-blockers (NSBB, eg. propranolol, nadolol) - OR - Endoscopic variceal ligation	• Start propranolol (20 mg b.i.d) or nadolol (20 mg q.d) • Titrate to maximum tolerable dosage or a heart rate of 55-60 b.p.m • No need for repeat endoscopy • Ligate every 1-2 weeks until variceal obliteration is achieved • First surveillance endoscopy 1-3 months after variceal obliteration, then every 6-12 months
Second line therapy (if combined pharmacologic + endoscopic treatment has failed)	- TIPS *or* - Shunt surgery (CTP class A patients, where available)	

Abbreviations: BID, twice daily; BPM, beats per minute; CTP, Child Turcotte Pugh; QD, once daily; NSBB, non-selective beta-blocker; TIPS, transjugular intrahepatic portosystemic shunt

Printed with permission: Macmillan Publishers Ltd: Garcia Tsao et al. *Am J Gastroenterol* 2009; 104:1802-1829, Table 3, page 1809.

- Approach for
  - Child A
    - NSBB or NSBB plus EVL (endoscopic variceal ligation; [depends on whether measurements can be done to assess ∆ HVPG])
  - Child C
    - EVL
      - No rebleeding
        - EVL repeated
      - Rebleeding
        - EVL + NSBB
    - Low risk
      - NSBB (non-selective beta blockers)
        - Small, medium or large EV, plus
        - Red wale marks; or
        - Child C or B cirrhosis
        - Benefits
          - ↓ progression of small to large EV
          - ↓ cumulative probability of EVB
    - High risk
      - NSBB (non-selective beta blockers)
        - ↓ MR (mortality rate) from EVB (5% versus 10% with placebo)
        - ↓ MR (trend) from all causes (21% versus 27% with placebo; or 0.7)

Abbreviation: ARR, absolute risk reduction; EV, esophageal varices; EVL, endoscopic variceal ligation; GV, gastric varices; HVPE, hepatic venous pressure gradient; NNT, numbered needed to treat; NSBB, non-specific beta-blocker

- Dosing
  - Starting dose of nadolol (NSBB)
    - MAP (mean arterial pressure)
      - < 85 mm Hg 20 mg po per day
      - > 85 mm Hg 40 mg po per day

- Titrate the dose of NSBB by
  - ↓ HR (heart rate) 15% to 20%, or < 55 bpm
  - ↓ HVPG (hepatic vein pressure gradient: PV pressure – HV pressure) 10% to 20%
  - EVL (endoscopic variceal ligation)
    - If NSBB fail to prevent enlargement of EV → EVL
    - EVL may be superior primary prophylaxis for large (F2 or F3) varices
- Repeat EGD
  - Cirrhosis
    - Compensated, q 2 - q 3 yr
    - Decompensated, q 1 yr
  - Note: once the patient has experienced EVB or has developed ascites, EGD is done annually

SO YOU WANT TO BE A GASTROENTEROLOGIST!

Nadolol and propranolol are non-selective beta blockers (NSBB) which reduce portal pressure mainly by ↓ WHVP (a surrogate for portal pressure). Carvedilol is a mixed adrenergic blocker, with both beta and alpha blocking activity.

- Give a **comparison** of the use of propranolol versus carvedilol for the primary prevention of EVB.

Endpoint	Propranolol	Carvedilol
○ Portal venous inflow	↓	↓
○ Hepatic vascular tone	-	↓
○ Reduction in portal pressure	13%	20%
– HVPG ≤ 12 mm Hg	14%	64%
– GFR	↓	-
– CO	↓	-
○ Plasma volume	-	↑
○ Rate of 1st EVB	23%	10%

Abbreviations: CO, cardiac output (a predictor of HRS [hepatorenal syndrome]); EVB, esophageal variceal bleeding; GFR, glomerular filtration rate; HVPG, hepatic venous pressure gradient

Clinical Tips

- In the patient with UGIB due to esophageal varices (5-30% of all cases of UGIB), adding octreotide plus infusion for 2-5 days after EHT improves the control of bleeding. Also, adding ceftriaxone or quinolones reduces bacterial infection (including SBP [spontaneous bacterial peritonitis]) and mortality (DeFranchis R. *J Hepatol* 2005:167-76.)
- Recurrent esophageal variceal bleeding in the Child-Pugh class A or B cirrhotic, which occurs despite repeated endoscopic variceal banding or maintenance use of nonselective beta blocker may require the placement of TIPS (transjugular intrahepatic postoperative shunt) or a distal splenerenal shunt (DSRS). The reintervention rate is much lower with DSRS than TIPS (82% vs 11%, likely due to the TIPS shunt stenosis), with no difference in rebleeding, hepatic encephalopathy or death (Henderson JM, et al. *Gastroenterology* 2006:1643-51.)
- Gastric varices due to splenic vein thrombosis can be cured by splenectomy.

➢ Pregnancy and bleeding EV

- Give the treatment of small esophageal varices found in a woman who is 12 wk pregnant.
  - Follow patient with a high-risk obstetrician
  - Do not undertake EBL (endoscopic band ligation), since these new yet small EV are from ↑ flow in the azygous system as a result of the expected ~ 50% ↑ cardiac output which occurs with normal pregnancy.
  - Under these circumstances, these EV do not usually bleed.
  - From the same reason, BB (beta blockers) do not need to be used for primary prophylaxis of the EV.
  - If for some reason the patient were on BB, these should be stopped in the third trimester, because of their risk to the fetus (development of bradycardia).

Beta blockers (BB) are efficacious to prevent primary and secondary bleeding from esophageal varices in persons with cirrhosis and portal hypertension.

- Give the management of the BB of the cirrhotic woman who becomes pregnant.

Trimester	FDA category
1	C
2 or 3	D

  - Intrauterine growth retardation
  - Bradycardia in the fetus

Ectopic Varices

- Definition
  - Ectopic varices are varices which occur at site other than the esophagus or stomach

- Give the treatment options for bleeding ectopic varices.

  - Treatment options
    - EVL
    - NSBB
    - Transhepatic embolization
    - TIPS
    - Surgical ligation
    - Selective surgical shunt e.g. splenorenal shunt

Abbreviations: EVL, endoscopic variceal ligation, NSBB, non-selective β-blockers; TIPS, transjugular intrahepatic portosystemic shunt

Please see Feldman M., et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. Saunders/Elsevier, Philadelphia, 2010, Figure 90-19, page 1514 for suggested "algorithm for the management of bleeding from ectopic varices in patients with portal hypertension".

TUMORS OF THE ESOPHAGUS

- Give the **Vienna Classification** of esophageal neoplasia based on the internationally accepted histopathologic evaluation of endoscopic mucosal biopsies.

Category		Histopathology
1	–	No dysplasia
2	–	Indefinite for dysplasia
3	–	Low-grade dysplasia (LGD) / adenoma (aka high-grade intraepithelial neoplasia)
4	–	High-grade dysplasia (HGD) / adenoma (aka high-grade intraepithelial neoplasia, non-invasive carcinoma, non-invasive epithelial neoplasia suspicious for invasive carcinoma)
5	–	Invasive epithelial neoplasia ▪ Intramucosal carcinoma (category 5.1) ▪ Submucosal carcinoma (category 5.2)

Note: there is high inter-observer variability (as reflected by low kappa [k] statistic) distinguishing category 4 from 5.1, and 5.1 from 5.2

```
                 k                    k
               0.42                 0.71
4 I----------------------------------5.1---------------------------------I 5.2
```

Vienna Category

- Using the **T-N-M Classification system**, give the mucosal (M) and submucosal (SM) sub-classification of esophageal tumors.

	Sub-classification		Tumor
(T1a)	M	1	Limited to epithelium
		2	Invades the LP (lamina propria)
		3	Invades into but not through MM (muscularis mucosa)
(T1b)	SM	1	Penetration into up to 1/3 of SM (< 500 µm)
		2	2/3
		3	3/3

Shown in brackets is the AJCC stage definition

Abbreviations: M, mucosa; SM, submucosal

- Diagnosis
  - Patients with new onset dyspepsia plus alarm symptoms ar any age, or new-onset dyspepsia at age ≥ 50 to 55 yrs must have an EGD
  - Atleast 6 mucosal biopsies must be taken from any suspicious mass lesion or stricture
  - Staging is performed with
    - CT multiplanar of chest, abdomen and pelvis
    - EUS (endoscopic ultrasound)
    - PET-CT scanning should be used in combination with EUS and CT for esophageal and for esophageal-gastric junctional tumor assessment
  - Diagnosis of high grade dysplasia should be made and confirmed by "… two histopathologists, one with special interest in gastrointestinal disease"

- Treatment
  - It is recommended that mucosal (M1 and M2, and possibly M3) tumors be treated by one form of EMR, and that the submucosal (SM1, SM2, and SM3) tumors be treated by esophagectomy.
  - Undertaken by experienced clinicians, preferably within the setting of a multidisciplinary team
  - Esophageal mucosal cancer

    EMR (endoscopic mucosal resection)
  - Gastric mucosal cancer

    EMR or ESD (endoscopic submucosal dissection)
  - Esophageal resection
    - Antithrombotic plus antibiotic prophylaxis
    - "… adequate longitudinal and radial resection margins ….. achieved with lymphadenectomy appropriate to the histological tumor type and location"
  - Chemoradiotherapy
    - Squamous
      - Localized
      - Proximal esophagus
        - Chemoradiation

        - Mid / distal esophagus
          - Chemoradiation, or
          - Chemoradiation plus resection
        - Non-localized
          - Resection
    - Adenocarcinoma
        - Preoperative plus post-operation chemotherapy plus resection
        - Pre-operative
          - Chemoradiation plus resection, or
          - Chemotherapy plus resection

- Palliation for symptom relief
    - External beam radiotherapy
    - Trastazmab, cisplatin / fluoropyrimidine for HER-2 positive EGJ adenocarcinoma
    - Brachytherapy for symptoms of life expectancy > 3 mon
    - Self-expanding stents for
        - Obstructing mass
        - Tracheo-esophageal fistulisation
        - Perforation
    - Laser therapy plus external beam radiotherapy or brachytherapy for
        - Exophytic tumor
        - Tumor growing into stent
    - Argon plasma coagulation for
        - Tumor above / below stent bleeding inoperable tumor

Source: Allum et al; Gut 2011; 60: 1449-1472.

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- Give the explanation for the possible **difficulty in distinguishing** histopathologically between M3 and SM1 BE (Barett epithelium) tumors.
    - M3 invades into but not through the muscularis mucosa (MM)
    - In BE, there may be both a superficial and a deep layer of the MM!
    - Infiltration through the superficial MM layer is M1, and only infiltration through the deeper SM layer represents invasion of the SM, and is therefore SM1.

- List 6 endoscopic imaging modalities for detecting/ staging esophageal neoplasia.
    - High resolution/high-definition/magnification endoscopy – white light high resolution endoscopy (HRHDME)
    - Chromendoscopy (CE) (combined with HRHDME) – Lugal's sphincter, toludine blue, methylene blue, indigo carmine, acetic acid, crystal violet
    - Narrow band imaging (NBI)
    - FICE (Fuijnon intelligent chromendoscopy; computed interval chromendoscopy)
    - Point spectroscopy – fluorescence, elastic scattering, RAMAN, multimedial
    - Autofluorescence imaging (LIFE, light -induced fluorescence endoscopy [FE]), drug-induced FE, video autofluorescence imaging)
    - Optical coherence tomography (OCT; micro CT)
    - Confocal endomicroscopy
    - EUS (endoscopic ultrasound)

Abbreviations: CE, chromendoscopy; CIC, computed interval chromendoscopy; FE, fluorescence endoscopy; FICE, Fuijnon intelligent chromendoscopy; HRHDME, white light high resolution endoscopy; LIFE, light -induced fluorescence endoscopy; OCT, optical coherence tomography

Printed with permission: Curvers WL, Kiesslich R, Bergman JJ. *Best Prac Res Clin Gastroenterol* 2008; 22(4):687-720.

ENDOSCOPIC ULTRASOUND (EUS)

- Advantages
    - Andosonography allows distinction between intramural and extramural lesions by examination to a depth of ~20 mm (gutwall is about 4 mm thick)
    - Allows localization of intramural lesion to a specific layer of intestinal wall.
    - Provides the means to obtain tissue for pathological examination by way of FNA (fine needle aspiration) or trucut biopsy for cytological examination.

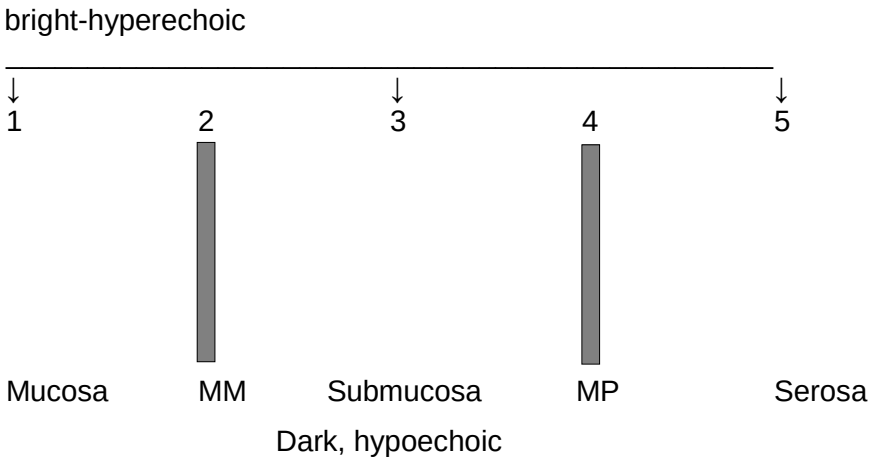
- Miniprobes may be passed through the working channel of a standard EGD, and provide more detail, but only for flat lesions or lesions < 1 cm.

- Basic of interpreting endoscopic ultrasound

  - Learn TAE-layers of the bowel wall to stage lesions by EUS

EUS layer	Anatomy	Echogenicity	Shading
1	Mucosa	↑	Bright
2	Muscularis	↓	Dark
3	Submucosa	↑	Bright
4	Muscularis propria	↓	Dark
5	Serosa	↑	Bright

- How to describe the EUS image
  - Size
  - Vascularity
    - Echogenicity
    - Hyperechoic
      - Bright
      - Intensity is similar to or greater than layers 2 and 4
        - 1 mucosa (superficial)
          - 3 submucosa
          - 5 serosa
    - Hypoechoic
      - Dark
      - Intensity similar to or lower than that of layers
        - 2 LP (lamina propria)
        - 4 M (muscularis propria)
    - Anechoic
      - Black, no internal echo
        - Intensity of water
        - Acoustic enhancement (a brighter echo behind a black fluid filled cyst, vessel or gallbladder



Abbreviation: MM, muscularis mucosa; MP, muscularis propria

- Overall accuracy of determining layer and location of tumor ~80%

➢ Localization of tumor by EUS may suggest its diagnostic pathology, e.g.

- (light) hyperechoic (1,3,5)
  - Usually a
    - Lipoma (especially when in Layer 3)
    - Duplication cysts in layer 3
- (dark) hypoechoic (2,4)
  - Usually a
    - Carcinoids NET (usually layer 2)
    - GIST (especially in 4)
    - Leiomyoma (especially in layer 4)
    - Cyst, filled with mucin, debris
    - Aberrant pancreas
    - Pancreatic pseudocysts
    - Granular cell tumors
- Anechoic
  - Black
  - Often associated with acoustic enhancement
  - Misclassifications in ~50% of hyoechoic tumor
- Esophageal varices appear anechoic (black) in EUS layers 2 and 3

MCQ ALERT

EUS layer	Most common abnormality
2	Carcinoid (NET) EV
3	Lipoma duplication cyst EV
4	Leiomyoma

Clinical Gem

Both esophageal varices and duplicaton cysts may appear in EUS layer 3

- Distinguish from esophageal duplication cyst using Doppler colour ultrasound

- Give 3 ways how **to increase the depth of a "mucosal" biopsy** (e.g. for a submucosal lesion)
  - EGD - tunnel biopsy (take a second biopsy from an initial biopsy site)
  - EMR - unroof the mucosa, biopsy submucosa
  - EUS - FNA, or trucut biopsy

  - Overall accuracy for determining malignant GIST
    - EUS 78%
    - EUS + FNA 91%
    - EUS + FNA + KL-67 ~100%

  - ESD - endoscopic submucosal dissection, including use of IT (insulated tip) knife for en bloc dissection

  - Suggestive of malignancy
    - Irregular extraluminal margins
    - Cystic space (heterogeneous)
    - Large associated lymph nodes

# of above findings	Sensitivity	Specificity	PPV
1	91%	88%	93%
2	-	-	100%

  - Benign tumor
    - Regular margins
    - Homogeneous
    - Size ≤ 3 cm
    - If all 3 above signs present , ~99% likelihood the GIST is benign
    - Note: GISTs > 1 cm have the potential to be malignant, so even if a GIST > 1 cm looks benign on EUS, perform annual EUS surveillance for assessment of possible change in size, or development of malignant EUS features
    - Irregular margins or heterogenous
    - Cystic spaces, or large associated lymph nodes

- Heterogeneous appearance of lesion on EUS
  - Especially when large and in esophagus – likely
    - Leiomyosarcoma
    - Lieomyoblastoma
  - May be due to associated
    - Liquefaction necrosis
    - Hyaline degeneration
    - Connective tissue
    - Cystic generation

GASTROINTESTINAL STROMAL (MESENCHYMAL) TUMORS (GIST)

- Esophagus
  - Leiomyomas
    - Commonest stromal tumor
      - Endogastric (grow into the lumen)
      - Mid- or lower- third of esophagus
    - Perform at least annual EUS for small tumors
  - Polypoid leiomyomas < 2 cm endoscopic snare resection
  - Surgical resection
    - Symptoms
    - > 1 cm
    - Structural changes from previous EUSs
  - Leiomyosarcomas
    - May require partial or total esohagectomy

- Stomach

- Pathology of GIST (gastrointestinal stromal tumors)
  - Site
    - Stomach ~70%
    - Small bowel ~25%
    - Colon / rectum 5%
  - Malignant potential
    - All GISTs > 10 mm

- Markers for GIST
  - C-kit (a stem cell factor receptor) (~99%)
    - CD34 (a hematopoietic cell progenitor cell antigen) (70%)
    - Smooth muscle actin (20% to 30%)
    - S 100 protein (marker of neural differentiation)
- Miscellaneous
  - Fat
    - Lipoma
    - Liposarcoma
  - Muscle
    - Leiomyomas
    - Leiomyosarcomas
  - Nerve
    - Schwannomas
  - Desmoid tumors
  - Endo- or exogastric (into or away from lumen, respectively)
  - Exogastric dislace rather than invade adjacent tissue
  - GIST and leiomyomas may be both endo- and exogastric, giving a dumbbell shape
  - GIT and leimyosarcomas
    - Usually exogastric
  - Leiomyomas are multiple in ~25%

- Genetic mutations
  - Mutational activation of genes
    - KIT
    - PDGFRA
    - DC117

- Diagnosis
  - EUS plus FNA

- Treatment
  - Medical treatment
    - TK (tyrosine kinase) inhibitors, e.g. imatimib, used as adjuvant or neoadjuvant therapy (before surgical resection)
      - GISTs ≥ 3 cm
      - ↓ GIST recurrence is post-op year 1

- Surgical treatment
  - Segmental resection enbloc for ≥ 2 cm; leaving the tumor pseudocapsule intact
  - Obtain negative tumor resection margins
  - Laparoscopic resection if possible
  - Consider using neoadjuvant therapy with imatinib

- **Postsurgical follow-up** (not evidence-based)
  - GIST
    - Clinical (history & physical) and CT scan q 3-6 mon for 5 yr; then q 1 year
  - Leiomyosarcoma
    - Clinical & CT
      - q 3 - 6 mon for 2 - 3 yr, then every year
      - Regular chest x-ray
    - If margins of resected leiomyosarcoma are positive, perform follow-up as above, only more intense longterm:
      - q 3 - 6 mon for 2 - 3 yr
      - q 6 mon for 2 yr, then every year

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- Give the management of the "**post-embolization syndrome**" (abdominal pain, nausea / vomiting, fever) associated with hepatic arterial embolization and chemoembolization for hepatic tumor (e.g. HCC, metastatic GIST).
  - Supportive care ~ only

OTHER TUMORS

- Lipoma
  - EGD/C
    - Single indentation of mucosa
    - Yellowish
    - Smooth
    - Easily indented (“pillow” sign, aka “cushion” sign; sensitivity of 40%, specificity of 99%)
    - Easily tented (mucosa can be pulled away from submucosal growth by gently tugging on mucosa biopsy forcep; known as “tenting” sign)
  - EUS
    - Layer 1,3*,5 (hyperechoic – light)

- Carcinoid tumor
  - EGD / commonest sites (in USA)
    - Appendix
    - Rectum — usually are single
    - Ileum
    - Stomach — often are multiple
  - EUS
    - Usually layer 2
    - Hypoechoic
    - Homogeneous

- Granular cell tumors (GCT; aka schwannoma)
  - Often in esophagus (mid- and lower- third)
  - EUS layer 2 or 3
  - Hypoechoic on EUS
  - Homogeneous
  - Usually benign unless > 4 cm
  - IHC (immunohistochemistry) S-100 protein positive

- Duplication cysts
  - Usually in proximal small intestine
  - May or may not communicate with the lumen

- Epithelium
  - Squamous
  - Columnar, or
  - Ciliated
- Contain mucoid fluid
- Usually benign

A patient is seen on EGD to have a small submucosal bulge in the duodenal wall. EUS is not available. CT scan confirms the pressure of a submucosal tumor.

- Give the characteristics of the CT scan which suggests that the lesion is a **pancreatic rest** rather than another type of submucosal tumor, and indication how certain you can be of the CT diagnosis of a pancreatic rest.

  - CT findings suggesting that a submucosal lesion is a pancreatic rest
    - Seen in duodenum, antrum or pylorus
    - Flat and oval shape
    - Fuzzy, poorly-defined border
    - Endoluminal growth
    - Mucosa over the submucosal tumor is markedly enhanced
  - Performance characteristics, depending upon number of above CT scan findings

Number of CT findings	Sensitivity	Specificity
2	100%	83%
3	100%	100%

Duplication cysts (DC) of the small intestine are usually in the submucosa (EUS layer 3), are anechoic, homogeneous, and have regular margins.

- Give the complications of a DC (duplication cysts) which may make it difficult on EUS or on CT scan to distinguish a duplication cyst from a solid malignancy.
  - A DC is, as the name implies, a cyst. However, it may become solid if
    - It undergoes malignant degeneration, and becomes solid
    - It may become filled with debris, and appear to be solid

On EUS of the esophagus, a duplication cyst (DC) is **anechoic**, homogeneous, has regular margins, and is usually seen in EUS layer 3.

- Give the name of a much more common anechoic lesion than DC seen on EUS of the esophagus, and name the diagnostic imaging test which helps to distinguish between these two lesions.
    - Esophageal varices are also anechoic and are seen in layers 2 and 3 on EUS
    - Dopper colour ultrasound will show flow in varices, but not in a duplication cyst.

- Pancreatic rest (aka ectopic pancreas, aberrant pancreas, heterotopic pancreas)
    - Comprised of cystically dilated exocrine cells
    - May undergo malignant degeneration
    - EGD
        - Submucosal tumor
        - Usually in antrum, duodenum, proximal small bowel
        - Central umbilication (from a draining duct)
    - EUS
        - Hypoechoic area rom pancreatic acinar cells
        - Anechoic area from draining duct
        - Heterogeneous
        - Fuzzy margins
        - Layer 3 or 4, or both 3 plus 4

"The difference between how a person treats the powerless versus the powerful is as good a measure of human character as I know."

Robert Sutton

STOMACH

DYSPEPSIA

- Demography
  - Annual occurrence in general public ~25%
- Definition
  - Dysplasia is pain or discomfort in the upper abdomen which may be associated with symptoms described as heartburn, indigestion, nausea, fullness, poor digestion.
  - Some definitions do not include heartburn.
  - Epigastric pain or burning (termed “epigastric pain syndrome”)
  - Postprandial fullness (termed “postprandial distress syndrome”)
  - Early satiation (meaning “inability to finish a normal sized meal or postprandial fullness)
  - Uninvestigated dysplasia
    - Blood work, ECG may be performed as needed, but the dyspeptic patient has not been investigated with an EGD (esophagogastro-duodenaoscopy)
- Clinical
  - There may also be “alarm symptoms” (suggesting possible esophageal or gastric malignancy):
    - **VBAD**
      - **V**omiting
      - **B**leeding – hematemesis, melena
      - **A**nemia
      - **D**ysphagia, odynophagia
  - There may be other associations which may guide the decision to earlier endoscopy
    - First Nations Aboriginal persons
    - Family recently imigragrated from areas with high risk of esophageal gastric cancer, or high prevalence of H. pylori infection
    - **FWLMS**
      - **F**amily history of upper GI cancer
      - **W**eight loss (non-intentional)
      - **L**iver disease
        - Jaundice
        - Ascites
      - **M**ass in abdomen or lymphadenopathy
      - Surgery on stomach in past (risk of stomal / “stump” cancer

- Note: the PPV (positive predictive value) of alarm symptoms is low, but the NPV (negative predictive value) is 99%; so, absence of “red flag” or “alarm” symptoms argues against upper GI malignancy being a cause of the patient’s dyspepsia.

- There is so much overlap in symptoms that it is not possible to confidently distinguish between the usual causes of dyspepsia (i.e. poor specificity)
  - GERD (gastroesophageal reflux disease)
  - PUD (peptic ulcer disease, comprised of DU [duodenal ulcer] and GU gastric ulcer])
    - DU classically, occurs
      - On an empty stomach
      - 2 to 3 hours pc, when buffering acid of food has been lost,
      - HCl secretion is no longer high between 11 pm to 2 am
      - Discomfortped by taking food

  - NERD (normal endoscopy reflux disease) and NUD (non-ulcer dyspepsia) describe the same condition of reflux-like dyspepsia and non-ulcer dyspepsia, as well as the epigastric pain syndrome and the post-prandialdistress syndrome in which the patient suffers from dyspepsia, but the EGD is normal
  - Thus NERD and NUD are forms of “investigated dyspepsia, ” since an EGD has been performed
  - NERD and NUD may also represent part of the spectrum of functional GI disorders
- Warning: exceptions – although the absence of “VBAD FWLML” is reassuring in the dyspeptic person, the presence of upper GI tract malignancy must be excluded by EGD in several circumstances:
  - Age over a cut-off (guidelines vary from 45 to 55 years of age; suggestion – use age 50, or earlier if one of the following is present)
  - Family or personal history of cancer of esophagus or gastric cancer (GCa)
  - Personal origin from an area of the world with a high incidence of GCa; e.g. Japan, Peru
  - Personal origin from an area or group of persons with a high prevalence of H. pylori infection (because H. pylori infection may be a factor causing GCa)

- The age cut-off is determined by the point at which the incidence of ECa / GCa begins to rise; e.g. 1% at age < 50 in N. Europe, USA, Canada
- Middle aged Caucasian male with > 10 year history of moderately severe GERD symptoms occurring ≥ 3 times per week (risk of Barrett esophagus and ECa)

- Also recall: the odds ratio of gallstones in a dyspeptic is low (~ 2.0 and even if the patient is shown to have gallstones on abdominal ultrasound, that is not sufficient proof that the dyspepsia is not caused by GERD, PUD, NERD / NUD, or ECA / GCa.
- Overlap with IBS symptoms
  - Dyspepsia in persons with IBS, 14%
  - Reflux-like dyspepsia in IBS, 32%
  - IBS in persons with dyspepsia, 37%

- Clinical approach
  - Age < 50 years, not in an "exception" group (FLMS), no alarm symptoms (VBAD) → empiric anti-secretory, or
  - T & T ("test and treat" for H. pylori) if in a high prevalence H. pylori area or group
  - Age > 50 years, in an "exception" group, or with alarm symptom(s) → EGD
  - There are pro's and con's for each approach
  - If patient is in a low H. pylori risk area or group, then T&T is not the preferred approach
  - For economic and availability reasons, the "scope [EGD] and treat" approach may not be viable, but there is some evidence that the anti-secretory pathway may not be the cheapest over the long run, and may not give the greatest improvement in the quality of life of the patient.

- Empiric therapy
  - Empiric anti-secretory approach with OTC (over-the-counter) antacids, H2RA (H2 receptor antagonists), and PPIs (proton pump inhibitors)
  - PPIs may already have been used by the patient before consulting a physician
  - In guidelines, by "anti-secretory trial of therapy" is usually meant to be a standard dose of any PPI, given po od ½ hour before breakfast, and taken for 4 to 8 weeks.

- Test-and-treat (for H. pylori)
  - Prevalence of H. pylori in Northern Europe / Canada is about ~25% (~10% amongst locally born children)
  - Distinguish between H. pylori infection and H. pylori disease, e.g. prevalence of H. pylori in Canadian adults is ~25%, but prevalence of GU / DU in dyspeptics, ~5% (by EGD)
  - The rest of improvement with empiric treatment of H. pylori infection in investigated dyspeptics is higher, in part because DU- and GU-associated disease is being treated, rather than just H. pylori-associated gastritis, the associated symptoms from which generally respond poorly to the eradication of H. pylori.
  - Hp tests have a sensitivity of ~95%, so before stating that a patient has a Hp negative duodenal ulcer, perform biopsy- and non-biopsy-based tests for Hp, and for biopsy-based ulcers, ensure that at least 6 gastric biopsies were taken (antrum, 2; angularis, 2; and body 2) within more than 2 weeks of stopping acid inhibitory therapy.
  - In the patient with a gastric ulcer, take 6 biopsies from the edge of the edge of the lesion looking for possible malignancy, as well as the 2-2-2 biopsies of the gastric antrum, angularis and body, note above.

Please see: Thomson ABR. Chapter 61. In: Therapeutic Choices. Grey J, Ed. 6th Edition, Canadian Pharmacists Association: Ottawa, ON, 2011, Table 1**:** Drugs used for Dyspepsia and Peptic ulcer disease, page 821.

Please see: Thomson ABR. Chapter 61. In: Therapeutic Choices. Grey J, Ed. 6th Edition, Canadian Pharmacists Association: Ottawa, ON, 2011, Table 2**:** Helicobacter pylori Eradication Regimen, page 824-825.

Please see: Thomson ABR. Chapter 62. In: Therapeutic Choices. Grey J, Ed. 6th Edition, Canadian Pharmacists Association: Ottawa, ON, 2011, Table 1**:** Parenteral Drugs used in Management of Upper Gastrointestinal Bleeding, page 833.

- Give the benefits and limitations associated with 5 interventional/ diagnostic approaches to the patient with dyspepsia who is under 50 years of age and who has no alarm symptoms.

Diagnostic approach	Benefits	Limitations
○ "Watchful waiting" only	– Patients with mild and transient symptoms are not prescribed medication or investigated	▪ No clinical studies.
○ Empirical Antisecretory therapy (PPI or H2RA)	– Addresses symptoms immediately – Documented effect on reflux symptoms and ulcer-related symptoms	▪ Recurrence after therapy is the rule. EGD is often only postponed, and may be false negative.
○ Treat based on clinical diagnosis	– Clinically meaningful. Low costs	▪ Unreliable.
○ Treat based on subgrouping and computer-based algorithms	– Clinically attractive. Low costs	▪ Does not reliably predict EGD diagnosis or response to therapy
○ H.*pylori* test-and-treat	– Infected patients with ulcer disease will have symptomatic benefits. Reduces endoscopy rates. Safe and cost-effective compared with endoscopy. – Possible reduced risk of later ulcer development.	▪ Low benefit in those without peptic ulcer disease will not benefit. Continuing or recurrent symptoms may frustrate patients and clinician
○ H.*pylori* test-and-scope	– Potential to reduce upper EGD rates in H. pylori low-prevalence areas	▪ Only meaningful if a decision about eradication therapy in infected patients is influenced by endoscopy result. ▪ Increases endoscopy demands. Not applicable in H. pylori-high prevalence areas
○ Early endoscopy	– Diagnostic "gold standard" – Might lead to reduced medication in patients with normal findings. – Increased patient satisfaction shown in some clinical trials.	▪ Invasive. Costly. ▪ About half of EGDs will be normal. ▪ Long waiting lists may lead to false negative results. ▪ Not the preferred option for many patients.

Adapted from: Bytzer P. *Best Pract Res Clin Gastroenterol* 2004; 18(4): 683.

Dyspepsia and Pregnancy

- Demography
  - Upper GI symptoms are common in pregnant women, and when EGD has been performed the findings are esophagitis (34%) and gastritis (25%).
  - Predictors of heartburn during pregnancy include young age of the mother, her parity, increasing gestational age, and the presence of heartburn before pregnancy (which occurs in 14% of mothers) (Marrero JM, et al. *Br J Obstet Gynaecol* 1992:731-4).
- Diagnosis
  - A symptom-based approach should be followed.
  - Endoscopy (EGD should be avoided unless absolutely necessy and under the advise on a high risk obstetrician.
- Treatment
  - Only calcium-containing antacids should be used for GERD symptoms, since aluminum-containing antacids may cause fetal neurotoxicity, alginic acid (Gaviscon, sucralfate) may cause fetal distress, and magnesium-containing antacids may cause a number of fetal disorders (renal stones, respiratory distress and cardiovascular impairment, and hypotemia, especially when used in higher doses for longer intervals).
  - The H2RA (other than nizatidine [FDA, C] and the PPIs (othe than omeprazole [FDA, C] may be used during pregnancy and lactation.
  - Nizatidine is not recommended for lactating mothers (FDA C, due to report of growth retardation of rodent pups)

- Give 4 factors to consider when performing an absolutely necessary endoscopy in pregnant women.
  - A strong indication is always needed, particularly in high-risk pregnancies
  - Whenever possible, endoscopy should be deferred until the second trimester
  - The lowest possible dose of sedative medication should be used (wherever possible FDA category A or B drugs)

- Procedure time should be short (should not be a “teaching case”)
- To avoid inferior venal cava (IVC) or aortic compression, the patient should be positioned in the left pelvic tilt or left lateral position
- Presence of fetal heart sounds should be confirmed before sedation and after the procedure
- Obstetric support should be immediately available
- No endoscopy should be performed in patients with obstetric complications (placental rupture, imminent delivery, ruptured membranes, or pre-eclampsia)

Printed with permission: Keller J, et al. *Nat Clin Pract Gastroenterol Hepatol* 2008; 5(8): 435.

H. PYLORI INFECTION

A MCQ scenario speaks to the need for it to be proven that a previous H. pylori infection has been eradicated. Given the need to be certain the test is not falsely negative, watch out for

- UBT – falsely negative if patient has been on PPIs, H2RA or antibiotics in the week before the test
- Biopsy (EGD necessary) – based techniques if the test will be falsely negative and the H. pylori may have migrated to the gastric body; biopsy need to be taken from mucosa of both gastric antrum and body before you may be confident that the pathology report of “no H. pylori seen” signifies that the infection has truly been cured, and that the H. pylori are not simply hiding in the mucus adjacent to the mucosa of the gastric body.

- Useful background
  - In persons with H. pylori (Hp) associated non-ulcer dyspepsia (i.e., no gastric or duodenal ulcer), eradication of Hp results in longterm symptomatic relief in only ~ 8% of patients
  - PMC (PPI – metronidazole – clarithromycin) and PCA (PPI – amoxicillin – clarithromycin) regimens are equivalent.
  - It is useful for the physician to have available date on the local rates of Hp resistance to clarithromycin.
  - “PPI – clarithromycin – containing therapy without prior individual susceptibility testing should be abandoned when the clarithromycin

resistance rate in the region is more than 15-20%" (Malfertheiner et al., Gut 2012; 61: 646-664).

- Smoking reduces Hp – eradication rates by about 8%
- Extending the duration of triple therapy with PMC or PAC from 7 to 10-14 days increases the Hp – eradication rate by ~ 5%
- Bismuth - containing quadruple therapy is also an alternate first-line empirical therapy since compliance with quadruple therapy is high and is particularly useful in areas of high clarithromycin resistance.

➢ Testing

- If using a biopsy-based test for H. pylori
  - Stop PPI for at least 1 week (preferably 2 wk) before taking EGD biopsy
  - Take 2 EGD biopsies from gastric antrum, 2 from body, and 2 from angularis
- Positive serology for H. pylori only indicates previous exposure; a negative serology test excludes H. pylori-associated infection.
- Specificity of serology is even lower with increasing age and in cirrhosis
- Determine presence of active infection with UBT or stool antigen test.
- If Hp – eradication fails with PMC or PAC, use
  - Bismuth – containing quadruple therapy, or
  - Levofloxacin – containing triple therapy (PLA [PPI, levofloxacin plus amoxicillin]) or PCL for 10 days, or
  - Sequence therapy (PA-PMC)
  - Concomitant therapy

"Be an advocate, seek something good for everyone: seek justice, peace, and love."

Grandad

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- Canadian guidelines recommend that a person with dyspepsia at age 50 or over, or dyspepsia at any age with alarm symptoms (vomiting, bleeding, anemia, dysphagia, weight loss) should have an EGD to diagnose the cause of dyspepsia.
- Unfortunately, the waiting time for an EGD may be very long (> 6 months), by which time an early gastric cancer (definition: "a cancer that does not invade beyond the submucosa regardless of lymph node involvement" (Feldman M., et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. *Saunders/Elsevier*, Philadelphia, 2010, page 900) may possibly have advanced.

- Give the reason why an upper GI (UGI) barium study is not recommended for investigation of dyspepsia, but is still understandably used for the at-risk dyspeptic patient waiting for EGD.
  - It has all to do with performance characteristics: the sensitivity and specificity of an UGI to detect advanced GCa is about 65%, and 90%, respectively. So, a negative UGI does not exclude a serious lesion, and certainly does not exclude EGCa (early gastric cancer), because the sensitivity is disappointingly low.
  - However, if the UGI shows a suspicious lesion thought to possibly be EGCa or EECa, with a specificity of ~ 90%, this information would be forwarded to the consultant and should inspire a prompt endoscopy.
  - For staging a GCa, the TNM system is used.
  - EUS (endoscopic ultrasound) is recommended to stage GCa, including EGCa (early gastric cancer).
  - This is because EUS has 90% accuracy to differentiate between mucosal and submucosal tumor invasion (note that accuracy for restaging T and N after neoadjuvant chemotherapy is lower, ~50%).

Peptic Ulcer Disease (PUD) Associated with H. Pylori Infection

- Give the role of MDCT (multi-detector row CT) in staging GCa.
    - MDCT "….appears to have comparable accuracy to EUS in terms of T and N staging" (Feldman M., et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. *Saunders/Elsevier*, Philadelphia, 2010, page 901).

    - H. pylori infection may be
        - Associated with, or causative of GU and DU
        - ↑ chance of developing ASA / NSAID-associated GU / DU
        - ↑ effect of smoking on slower healing, and higher risk of relapse of ulcer

      (Note: once associated H. Pylori infection has been cured, smoking loses these adverse effects on ulcer healing and relapse):
        - ↑ risk of ulcer relapse (80% for H. pylori +, 10% for H. pylori-)

    - Combine anti-H. pylori therapy with PPI to
        - ↑ anti-H. pylori effect of antibiotics
        - Accelerate improvement of ulcer healing and symptom relief
    - Optimal pH for outcomes for different conditions (18 hours per day)

≥ 3	GU, DU
4	GERD
5	H. pylori eradication
6	Non-variceal upper GI bleeding (NVUGIB)

➢ Pharmaceutical therapy

- Uncomplicated peptic ulcer
    - PPI of your choice bid po for 2 weeks with 2 antibiotics (PMC, PAC) followed by PPI od for 2 weeks
    - If patient experiences frequent recurrences
        - Perform UBT with patient off PPI and antibiotic for 1-2 wk
        - If UBT positive, retreat H. pylori
        - If UBT negative, consider PPI po od continuously as maintenance therapy

- Complicated peptic ulcer
  - Complications of hemorrhage, obstruction, perforation
  - Treat PUD plus H. pylori infection as above for uncomplicated ulcer
  - Either repeat UBT off PPI therapy to prove eradication of H. pylori, with no PPI maintenance therapy (PPI po od), or
  - PPI maintenance therapy (PPI od), because of
    - High risk of reinfection with H. pylori
    - High risk of reulceration even without reinfection with H. pylori
    - Possibility that the original ulcer may have been caused by ASA / NSAIDs plus H. pylori infection

- Caution alert
  - Every patient being considered for long-term use of ASA / NSAIDs / Coxibs should be tested (by UBT) and heated for H. pylori of positive
  - Depending upon patient (host) and medication considerations, some persons on long-term on PPI po od, even after eradication of any associated H. pylori infection.

- Only calcium-containing antacids should be used for GERD symptoms, since
  - Aluminum-containing antacids may cause fetal neurotoxicity,
  - Alginic acid (Gaviscon, sucralfate) may cause fetal distress
  - Magnesium-containing antacids may cause renal stones, respiratory distress and cardiovascular impairment, and hypotemia.

- Non-eradication of H. pylori with standard triple or quadruple therapy
  - Confirm perisitence of infection
  - Confirm patient adherence to treatment recommendations
  - If local antibiotic resistance to H.pylori known, use this information to guide therapeutic decisions
  - If initial therapy for 7 days, consider repeat for 14 days

- Consider switching PAC to PMC or PMC to PAC, use a second round same therapy but for 14 days, or bismuth-based first-line therapy, or second-line therapies (with levofloxacin plus ampicillin, sequential therapy (PA-PMC), or concomitant therapy (PMCA).

- Treatment

  - If Hp – eradication fails after first and then second line treatment, subsequent treatment

    "…should be guided by antimicrobial susceptibility testing, whenever possible".

  - For persons who cannot take amoxicillin (penicillin allergy), use PCM or bismuth – containing quadruple therapy

  - Concomitant therapy (CT) is comprised of PPI, clarithromycin, metronidazole, amoxicillin (PMCA)
    - More effective than standard triple therapy (pooled OR, 2.86), and is less complex for the patient to take than is sequential therapy (ST)
  - Sequential therapy (ST) is comprised of PA-PMC
    - PPI bid plus amoxicillin (PA) 1 gm bid for 5 days, followed by
    - PPI bid plus clarithromycin 500 mg bid plus metronidazole or tinidazole bid for the next 5 days
    - The place for ST in guidelines remains to be established.

An MCQ is directed at the issue of the recommended follow-up of a dyspeptic < 55 years whose UBT is positive and they are given successful triple therapy for H. pylori. You are tempted to answer that the correct follow-up is to repeat the UBT to determine if the infection has been eradicated.

Wrong. Successful triple therapy for H. pylori in this setting means the patient has lost her / his dyspepsia. The only circumstances were the UBT must be repeated is

- Persistent dyspepsia
- The patient with complicated H. pylori-associated peptic ulcer (e.g. hemorrhage) must be proven by repeat testing that the anti-H. pylori treatment has effectively eradicated the bug (expected cure rate for triple therapy is only 80%)

Helicobactor Pylori-Negative Peptic Ulcer Disease

- The proportion of all peptic ulcers which are H. pylori-negative is increasing (~25%)
- Ensure that if the diagnosis of H. pylori infection is based on UBT or gastric mucosal biopsies, anti-secretory therapy must be stopped at least 1 week before taking gastric mucosal biopsies from antrum (2), body (2), and angularis (2).
- Before deeming that the patient has an H. pylori-negative peptic ulcer disease, care must be taken to exclude
  - H. pylori infection, using 2 different types of standard tests
  - Use of ASA, NSAIDs, Coxibs, bisphosphonates (check platelet aggregation or thromboxane B2 levels)
  - Fasting hypergastrinemia (ensure patient not currently taking anti-secretory therapy)

- Give 3 points which support the statement that H. pylori-negative (HpN) peptic ulcers are more serious / severe than are H. pylori-positive peptic ulcers (HpP).

Clinical	HpP	HpN
– Bleeding ulcer	4%	50%
– Recurrent ulcer bleeding	11%	42%
– ASA risk ≥ grade 3	18%	~50%
– Overall mortality rate	37%	88%

Abbreviations: ASA, American Society of Anesthesiologist

➢ Theories why HpN more serious than HpP GU / DU

- H. pylori involving the gastric body may ↓ secretion of HCl from parietal cells.
- H. pylori itself may have an anti-secretory effect, making PPI therapy more efficacious.
- The abnormalities in gastric acid secretion and in gastrin metabolism may be worse or different in HpN versus HpP peptic ulcer disease.

An uncerstanding of gasric parietal cell secretion of HCl and G cell secretion of stimulatory gastrin as well as D cell secretion of inhibitory somatostatin, is important to understand the pathophysiology of UD, as well as the gastric effects of hypergastrinemia, including the ZES (Zollinger-Ellison Syndrome) of the sporatic or MEN- / types.*ƒ*

Gastric Acid Secretion: understanding the basis for acid-lowering therapy

There are redundant and overlapping pathways for acid secretion and inhibition.

- Parietal cell
  - Secretory vesicles are lined with membrane containing the H+ / K+-ATPase acid-secreting pump.
  - With food stimulation the secretory vesicles traffic to and incorporated into the luminal membrane of parietal cells, forming the secretory canaliculi.
  - The pathway for K+ to reach the H+ - K+ ATPase is in a short-circuited state in fasting state, but upon stimulation this pathway allows access of the K^+ to the H^+ - K^+ ATPase, exchange of H^+ for K^+ and thus HCl secretion.
  - The parietal cell is stimulated by the cephalic, gastric and intestinal components, with activation occurring through
    - ↑ Ca^{2+} (intracellular Ca^{2+})
    - ↑ cAMP → cAMP-dependent PK (protein kinase) cascade
  - When activation of the parietal cell causes, or inhibition increases, the H^+-K^+ ATPase moves back (reinternationalization) into the cytoplasmic side of the parietal cell.
  - Reinternalization of the H^+ - K^+ ATPase occurs by way of the cytoplasmic tail of the beta subunit of the enzyme.

- Gastrin and Gastrin Receptors
  - Gastrin is released from G cells in the gastric antrum as a result of amino acids (AA) in the stomach (as well as protein and peptides), and from distention of the stomach.
  - Gastrin receptors
    - CCK2 (aka CCK-B, or gastrin) receptors in body of stomach on
      - Parietal cells
      - ECL cells, adjacent to parietal cells
    - CCK1 (aka CCK-A) receptors on D cells, pancreas, gallbladder and brain

- Gastrin
  - Acutely
    - ↑ histamine releases from ECL cells → histamine stimulates H2 receptor of parietal cells to secrete HCl
    - Releases ↑ histamine synthesis in ECL cells
    - Releases somatostatin (more from CCK rather than gastrin) → ↓ histamine release from ECL cells
    - Stimulation of ECL cells to release histamine
      - Gastrin
      - PACAP (pituitary adenylate cyclase-activating polypeptide)
      - VIP (vasoactive intestinal peptides)
    - Antigens stimulate gastric mucosal mast cells – release of histamine
  - Chronically
    - Causes hypertrophy of parietal cells and ECL (enterochromaffin-like) cells
- Other peptides which inhibit acid secretion by way of ↓ ECL histamine release from ECL histamine release
  - CGR (calcitonin gene-related peptide)
  - PYY (peptide YY)
  - Prostaglandins
  - Galanin
- CCK2 and CCK2 receptors are G-protein-coupled receptors
- Signaling by way of pertussis toxin-insensitive G-proteins
- Agonist stimulation of receptors
- Distention
  - Initially, little distention
    - VIP neurons are activated to release somatostatin
    - Somatostatin inhibits antral G cells
  - Then, more distention
    - Stimulation of release of acetylcholine (Ach; cholinergic)
      - Directly stimulates M3 receptors on parietal cell
      - ↑ gastrin
      - ↓ somatostatin
- AA in stomach
  - Direct effect of AA → G cells → ↑ gastrin
  - Indirect effect of AA
    - Activate Ach neurons
    - Activate GRP (gastrin related peptide) neurons → G cells → ↑ gastrin

- Note paradoxical effect of gastrin
  - ↑ histamine release from ECL cells
    - ↑ HCl secretion
  - ↑ somatostatic release from D cells
    - ↓ G release
    - ↓ HCl secretion

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Histamine released from ECL cells stimulates the H2-receptors on the basal membrane of gastric body parietal cells, increasing HCl secretion. Histamine also stimulates H3 receptors to ↑ HCl secretion.

- Give the mechanism of action of the H3 receptors to ↑ gastric HCl secretion.

  - Histamine stimulates H3 receptors to ↓ secretion of somatostatin from D-cells; the ↓ somatostatin leads to ↓ inhibition of somatostatin-associated parietal cell acid inhibition, and thus there is ↑ HCl secretion.

➢ Somatostatin

- Give 4 factors responsible for increasing and/or decreasing the **release of somatostatin** from the D cells.

  - ↑ release
    - Gastric acidity (↑ H+ → somatostatin → ↓ H+ [feed-back loop])
    - Minor distention of stomach, acting through VIP neurons
    - ↑ VIP activation
    - ↑ gastrin → ↑ somatostatin
      - ↓ ECL secretion of histamine
      - ↓ gastrin release
    - Major inhibitory mechanism of somatostatin
      - Reduction of gastrin-stimulated release of histamine from ECL cells
  - ↓ release
    - Major distention of stomach
    - Ach (acetylcholine)

- Prostaglandins
  - Produced and stored in gastric macrophages and capillary endothelial cells.
  - ↓ acid secretion by way of inhibiting
    - Gastrin-stimulated histamine release
    - Histamine-stimulated parietal cell acid secretion

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PYY (peptide YY) is contained in ECL cells in the terminal ileum and colon. Resection of the terminal colon (R. hemicolectomy) may be associated with increased gastric acid secretion, which sometimes results in diarrhea which responds to the use of a PPI.

- Give the mechanism of the increased acid secretion associated with performing a right hemicolectomy
  - PYY inhibits gastrin-stimulated histamine release
  - This inhibition is lost with ileal resection and R. hemicolectomy

- Pepsinogen
  - The secretion of pepsinogen from gastric body chief cells is increased by
    - Ach
    - Gastrin / CCK
    - Secretin
    - VIP

- Give the explanation why secretion of pepsinogen is essential for normal secretion of gastric acid, and why secretion of gastric acid is essential for normal function of pepsinogens.
  - Pepsinogens are converted to pepsins, which begin the process of digestion of dietary proteins to amino acids (AA).
  - AA directly stimulate G cells to ↑ gastrin, and indirectly activated Ach neurons as well as GRP neurons.
  - This ↑ gastrin leads to ↑ histamine released from ECL cells, which in turn stimulates the H2 receptors on the parietal cell to stimulate secretion of H^+.
  - Pepsins become inactive at pH > 4, so the low intragastric pH (↑H+) maintains pepsins in an active form, which then maintains the AA-stimulation of release of gastrin from G cells, as well as release of Ach and GRP from neurons.

Gastrinoma and Zollinger-Ellision Syndrome (ZES)

➢ Pathology

Hyergastrinemia and hypersecretion of gastric acid may occur with sporatic gastrinoma, or with a gastrinoma-associated with MEN-1 (multiple endocrine neoplasia type 1).

- Give the tumours found in patients with multiple endocrine neoplasia-type I (MEN-1), and their approximate frequency % is shown.

➢ Tumours	Approximate frequency (%)
o Parathyroid	90 (78-97)
o Pancreatic endocrine tumour	80 (81-82)
- Gastrinoma	54
- Insulinoma	21
- Glucagonoma	3
- VIPoma	1
o Pituitary tumours	40 (21-65)
- Prolactin-secreting	30 (15-46)
- Growth-hormone secreting	16 (6-20)
- Cushing's syndrome	16
o Adrenal cortical adenoma	30 (27-36)
o Thyroid adenoma	20 5-30)

o Parathyroid ~100% for symptomatic hypercalcemic patients, parathyroid gland removal, parathyroid autograft ± cervical thymectomy

o Pancreas
  - ~80% of MEN-1 patients
  - 40% have asymptomatic ↑ gastrin (serum), or ZES

o Pituitary adenomas, ~20% (usually a lactotroph adenoma)

- Location of gastrinomas
  - Parts of the duodenum (D)
    - D1 56%
    - D2 36%
    - D3 6%
    - D4 6%

Hypergastrinemia and hypersecretion of gastric acid may occur with sporatic gastrinoma, or with a gastrinoma-associated with MEN-1 (multiple endocrine neoplasia type 1).

- Give differences between **sporatic versus MEN-1-associated gastrinomas**.

Clinical	Sporatic	MEN-1 associated
Carcinoid tumors (NET)	~1%	30%
Number	Often single	Often multiple and in different sites
Site, gastrinoma triangle	80%	Pancreas, duodenal wall
Growth rate of metastases	Rapid	Slow
Consider exploratory laparotomy with curative intent when no evidence of metastatic disease	Yes	No
Surgical cure (duodenotomy and subtotal pancreatectomy)	50%	No definitive evidence of benefit of surgery
Liver metastases at diagnosis	~24%	6%
Survival overall		100% at 15 years
Identification of source of excess gastrin	Yes	No – imaged tumors may not be source of ↑ gastrin
Family history	No	Yes

Abbreviation: NET, neuroendocrine tumor

➢ Clinical

- Give the presenting features of ZES, and their approximate frequency.
  - Abdominal pain (75%-100%)
  - Pain and diarrhea (55%-60%)
  - Diarrhea (alone < 35%)
  - Heartburn (44%-64%)
  - Duodenal and prepyloric ulcers (71%-91%)
  - Multiple ulcers in unusual places
  - Stomal ulcers
  - PUD refractory to treatment
  - Ulcer complications (bleeding, 1%-17%; perforation, 0%-5%, or obstruction, 0%-5%)
  - Associated with MEN1 (22%-24%)

Abbreviations: MEN, multiple endocrine neoplasia; PUD, peptic ulcer disease; ZES, Zollinger-Ellison syndrome

Adapted from: Metz DC, and Jensen RT. *Gastroenterology* 2008;135:. 1469.

- Give the investigation of the patient with **fasting hypergastrinemia**, performed after a detailed history and physical examination.

  - Laboratory tests
    - Confirm fasting state for gastrin measurement
    - Calcium, PTH, TSH
    - Creatinine (exclude renal failure)
    - Chromogranin A
    - Urinary metanephrins
    - Schilling test, serum B_{12}

  - Provocative tests
    - Secretin infusion (paradoxical ↑ gastrin in ZES, >120 pg/ml; sensitivity 94%, specificity 100%)
    - Ca^{+2} infusion (marked increase in serum gastrin)
    - Basal and pentagastrin stimulated acid secretion (↑↑ BAO), BAO/MAO>60% (ZES) (↑ BAO $\geq$15 mEq/h without previous gastric surgery; $\geq$ 5mEq/h with preious gastric surgery)
    - Food-stimulated acid secretin (G-cell hyperplasia/ hyperfunction)

- Endoscopy
  - EGD
    - Multiple ulcers in unusual sites
    - Biopsy antrum for G-cell number (to distinguish between G-cell hyperplasia [↑G-cell number] vs G-cell hyperfunction (normal G-cell number); H. pylori
    - Thick gastric folds
  - EUS for possible tumour localization (especially in head of pancreas)
- Diagnostic imaging
  - Abdominal ultrasound
  - CT/ MRI, head (pituitary fossa, tumour in MEN I)
  - Ostreotide scan
  - MBIG scan
  - CT scan of abdomen
  - MRI of abdomen
  - Parathyroid scan

Abbreviations: EUS, endoscopic ultrasound; ZES, Zollinger-Ellison syndrome

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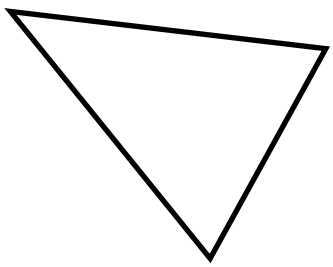
Most gastrinomas occur in the “gastrin triangle”.

- Give the landmarks of the gastrin triangle
  - The triangle is made up of the following 3 junctions:

Cystic duct/ CBD



Pancreatic neck/body

Abbreviations: CBD, common bile duct; D2,3, junction of the first and second parts of the duodenum

- Give the treatment of gastric hypersecretion due to ZES (Zollinger-Ellison Syndrome).

Optimal outcome is to reduce acid secretion to < 10 mEq/h, measured just before the next planned dose of PPI, so as to ↑ healing and ↓ recurrence of peptic ulvers, and their complication

- Tumor <2 cm
- Resection of tumor > 2 cm
- Parathyroidectomy (if ↑ PTH)
  - Control symptoms
  - Prevent complications (hemorrhage, obstruction, perforation)
  - Control gastrin-producing tumor (gastrinoma)
- Give oral PPIs in doses adequate to
  - Achieve optimal acid control

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Normally, secretin in the blood stream decreases gastric antral ECL (enterochromaffin like cell) secretion of SST (somatostatin) as well as gastrin.

- Give the explanation why the opposite is the effect in ZES for the secretin stimulated gastrin test in ZES.
  - Normally, secretin → ↑ SST, ↓ gastrin from antral G cells
    - The balance is ↓ gastrin
  - In ZES, there is secretion of such large amounts of gastrin that the gastrin-lowering effect of the SST on the G cells is so small that the serum gastrin level rises.
  - Because of the lack of effect of the SST in ZES (loss of functionally coupled SST cells), there is a positive effect of the exogenous secretion on serum gastrin levels.

- Therapeutic options directed at the metastatic liver disease include
  - Resection
  - Embolization of the hepatic artery ± chemotherapy
  - Radiofrequency ablation (RFA) or cryoablation ± surgical debulking

- Systemic chemotherapy
  - Streptozocin
  - Doxorubicin
  - Temozolomide
  - mToR (mammalian target of rapamycin)
  - TK (tyrosine kinase) inhibitors
  - Peptide receptor radioligand therapy

- In patients with metastatic gastrinoma, there may be some benefit from external beam radiotherapy, and some gastrinoma with somatostatin receptor-positive tumors benefit from octreotide or lanreotide-SR for control of symptoms.

Clinical Cautions

- Because of prolonged hypergastrinemia in sporatic gastrinoma, there may be hypertrophy of the parietal cells even when gastrin levels have returned to normal.
- As a result, even after a curative resection for a sporatic gastrinoma, the intragastric rate of acid secretion need to be monitored and the dose of continued PIs altered to keep gastric acid secretion below 10 mEq/h as measured just before the next dose of PPI.

➢ MEN-1 associated tumors

- Parathyroid ~100% for symptomatic hypercalcemic patients, parathyroid gland removal, parathyroid autograft ± cervical thymectomy
  - The hypercalcemia (↑ Ca^{2+}) in hyperparathyroidism may ↑ serum gastrin → ↑ parietal cell secretion of H^+
  - Coreect the hypercalcemia, and the serum gastrin and gastric secretion may return to normal
  - If this is the case, then there is no need to search for another explanation for the hypergastrinemia
- Pancreas
  - ~80% of MEN-1 patients
  - 40% have asymptomatic ↑ gastrin (serum), or ZES
  - Control acid secretion
- Pituitary adenomas, ~20% (usually a lactotroph adenoma)

NON-VARICEAL UPPER GI BLEEDING (NVUGIB)

- Demography
  - The overall incidence of hospitalization for UGIB is 134 per 100,000 population; incidence was higher among men than women (153 vs. 117 per 100,000)
  - UGIB incidence, but not mortality is associated with socio-economic status
  - Overall case fatality rates at 30 days after hospital admission is 10%; fatality rates rose with age and are higher for men than women, and for those with (vs. without) comorbid illnesses.
  - Adjusted fatality rates are 13% higher for patients admitted on weekends than on weekdays, and 41% higher for patients admitted on holidays than on weekdays (it is speculated that this difference in mortality could be attributed to reduced staffing and lack of availability of endoscopy on weekends and holidays in some hospitals)
  - A negative NG aspirate in the patient who presents with melanoma or hematoschezia reduces the likelihood of an upper GI source of the bleeding, but because of curling of the tube or duodenal bleeding which does not reflux into the stomach, 15-18% of persons with an upper GI source for bleeding will have a non-bloody aspirate.

Abbreviations: NNT, number needed to treat; TIPS, transjugular intrahepatic portosystemic shunt; UGIB, upper GI bleeding

- Assessment of risk (severity)

- Give 6 factors which are predictive of a poor prognosis after hemorrhage from peptic ulcer.

- Clinical
  - Increasing age
  - Increasing number of comorbid conditions (especially renal failure, liver failure, heart failure, cardiovascular disease, disseminated malignancy)
  - Shock – hypotension, tachycardia, tachypnea, oliguria on presentation
  - Red blood in the emesis or stool
  - Multiple of units of blood transfused
  - Onset of bleeding in the hospital
  - Need for emergency surgery
  - Anticoagulant use, glucocorticosteroids

Abbreviations: NVUGIB, non-variceal upper GI bleeding

- Laboratory
  - Coagulopathy
  - Multiple transfusions required
- Endoscopy
  - Higher lesser curve gastric ulcer (adjacent to left gastric artery)
  - Posterior duodenal bulb ulcer (adjacent to gastroduodenal artery)
  - Endoscopic finding of active arterial or venous bleeding or visible vessel (Forrest class Ia, Ib, and IIa lesions)

Printed with permission: Barkun A, Bardou M, Marshall JK. Consensus recommendations for managing patients with non-variceal upper gastrointestinal bleed. *Ann Intern Med* 2003; 139: 843-57, Table 19-4.

- Non-endoscopic **clinical** method to estimate volume depletion in NVUGIB

Clinical	Class I	Class II	Class III	Class IV
– Blood loss (mL)	< 750	750-1500	1500-2000	>2000
– Blood loss (% blood volume)	< 15	15-30	30-40	> 40
– Heart (beats/min)	< 100	>100	>120	>140
– Blood pressure	Normal	Normal	Decreased	Decreased
– Pulse pressure	Normal or increased	Decreased	Decreased	Decreased
– Ventilatory rate (breaths/min)	14-20	20-30	30-40	> 35
– Urine output (mL/h)	> 30	20-30	5-15	Negligible
– Mental status	Slightly anxious	Mildly anxious	Anxious and confused	Confused and lethargic
– Fluid replacement	Crystalloid	Crystalloid	Crystalloid and blood	Crystalloid and blood

Printed with permission: Atkinson RJ and Hurlston DP. *Best Pract Res Clin Gastroenterol* 2008; 22(2): pg. 234.

- Give the performance characteristics of vital signs and acute blood loss.

Physical Finding	Sensitivity (%)		Specificity (%)
	Moderate Blood Loss	Large Blood Loss	
○ Postural pulse increment ≥30 bpm or severe postural dizziness	7-57	98	99
○ Postural hypotension (≥ 20 mm Hg decrease in SBP)	9	...	90-98
○ Supine tachycardia (pulse > 100 bpm)	1	10	99
○ Supine hypotension (SBP < 95 mm Hg)	13	31	98

Abbreviations: bpm, beats per minute; SBP, systolic blood pressure

Adapted from: McGee S. R. Evidence Based Physical Diagnosis. 2nd Edition. *Saunders/Elsevier,* St.Louis, Missouri, 2007, Table 15.2 pg. 167.

➢ Clinical and endoscopic methods

In the patient with UGIB (upper GI bleeding) and with signs of **chronic liver disease**, give the patient

- ○ Octreotide sc 50-100 mcg bolus, then 25 mcg / hr for up to 3 d
- ○ Antibiotics (fluoroquinolone) before and 7 days after UGIB if EV is found
- ○ While recurrent EV bleeding is common, EGD must be performed with each presentation since just because EV are present does not mean they have bled.
- ○ Characteristic signs on the varices and seen on EGD will establish whether the acute UGIB in the patient with liver disease or known EV arose from
  - Bleeding EV
  - Peptic ulcer disease
  - Mallory-Weiss tear
  - Portal hypertensive gastropathy
  - GAVE (gastric antral vascular ectasia)
  - Dieulafoy lesion

- Give the rates (%) of rebleeding, surgery and mortality, without and with endoscopic hemostatic therapy (EHT), using the Forrest classification of bleeding peptic ulcers.

➢ Endoscopic method

EGD appearance	Prevalence on presentation	Rebleeding Rate (%) No EHT EHT(~70%↓)		Surgery Rate (%) No EHT EHT (~80%↓)		Mortality rate (%) No EHT EHT (~50%↓)	
Forrest Classification		EHT°	EHT⁺	EHT°	EHT⁺	EHT°	EHT⁺
○ Active Bleeding (Ib, ouzing)*	18	55	20	35	7	11	<5
○ Visible vessel (IIa); not bleeding	17	43	15	34	6	11	<5
– Adherent clot (IIb)	15	22	5	10	2	7	<3
– Flat pigmented spot (IIc)	15	10	<1	6	<1	3	<1
○ Clean ulcer base (III)	35	<5	<1	<1	<1	<1	<1

*Forrest 1a, active bleeding (spurting)

- ○ Overall benefit of EHT, ~2/3 ↓ in risk of rebleeding, surgery, death
  - – OR for use of EHT in high-risk lesions
    - ▪ Recurrent bleeding, 0.46
    - ▪ Need for surgery, 0.59

Abbreviation: EHT, endoscopic hemostatic therapy

Printed with permission: Atkinson RJ and Hurlstone DP. *Best Pract Res Clin Gastroenterol* 2008; 22(2): pg. 235; Enestvedt BK, et al. Gastroentest Endosc 2008;67:422-9.

- The **Rockall Risk Score Scheme** for assessing prognosis in patients with NVUGIB (PUD), using clinical and endoscopic considerations

	Rockall Risk Score			
Variable	0	1	2	3
○ Age (years)	< 60	60-79	≥ 80	≥ 80
○ Shock vital signs	SBP ≥ 100 mmHg, PR < 100 bpm	SBP ≥ 100 mmHg, PR ≥ 100 bpm	SBP < 100 mmHg, PR ≥ 100 bpm	SBP < 100 mmHg, PR ≥ 100 bpm
○ Comorbidity	None	None	Cardiac failure, ischemic heart disease, any major comorbidity	Renal failure, liver failure, disseminated malignancy
○ Diagnosis at time of endoscopy	Mallory-Weiss tear, or no lesion identified and no stigmata of recent hemorrhage	All diagnoses except malignancy	Malignancy of the upper GI tract	-
○ Stigmata of recent hemorrhage	None, or dark spot only		-Blood in upper GI tract -Adherent clot -Visible or spurting vessel	-

Maximum score prior to endoscopic diagnosis=7, maximum score following diagnosis=11

Abbreviations: GI, gastrointestinal; NVUGIB, non-variceal upper GI bleeding; PUD, peptic ulcer disease; PR, pulse rate

➢ Treatment

- Give the management of NVUGIB (non-variceal upper GI bleeding).
  - Stabilize ABC's
  - IV fluids, including blood
    - PRBC, packed red blood cells
    - Target hemoglobin concentration 90 g/dL
  - O_2 by nasal probes / mask, as indicated
  - Routine blood work, including CBC, electrolytes, Cr / BUN, Les and INR

- Monitor renal function and adequacy of fluid replacement
- Risk stratification
  - Without / before EGD Blatchford score
  - With / after EGD Rockall score
  - Speculated mechanism
    - Need for surgery, 0.59
    - ↑ activity of platelets
    - ↓ peptic digestion of clot

➢ Acid inhibition

- Continuous IV PPI IV infusion is given after EGD, and EHT (endoscopic hemostatic therapy) for Forrest lesions Ia, Ib, IIa) to ↓ risk of rebleeding surgery, or death.
  - High stigma lesion, continuous 72 hr IV infusion for 3 days, followed by PPI po, duration depending upon lesion
  - Low risk lesion once identified by EGD, discontinue, IV infusion and switch to PPI po, for duration dependent upon diagnosis of cause of NVUGIB.

- Give the reason why a person with isolated IgA deficiency should not be given a blood transfusion.
  - The patient would likely have IgG and IgE antibodies (anti-IgA antibodies), which would react against the IgA in the transfused blood, just as would happen with IV immunoglobulins.

- If a blood transfusion is contraindicated in a person with isolated IgA deficiency, give what is done if an urgent situation is faced and a blood transfusion would be life-saving.
  - The RBCs may be washed, removing most of the serum containing the IgA in the blood to be transfused. The washed and packed RBC may then be given safely.
  - May given before EGD to “down grade” Rockall risk score: 80 mg IV bolus over 30 min, then 8 mg/hr
  - RCTs show that adding bolus plus infusion of PPI to endoscopic hemostatic therapy (EHT) significantly decreased bleeding (NNT, 12) surgery (NNT, 28) and death (NNT, 45) (Laine L, et al. *Clin Gastroenterol Hepatol* 2009:33-47).

- Oral PPIs
  - Use high dose oral PPI to approximate IV PPI infusion e.g. lansoprazole 30 mg tabs 4 po, then 30 mg tabs 1 p q 30 min po.
- Octreotide and somatostatin
  - Potential explanation for clinical benefit
    - ↓ splanchnic blood flow
    - ↓ gastric acid secretion
    - ↑ gastric cytoprotection
  - Usually reserved for treating bleeding esophageal varices
    - For NVUGIB (non-variceal upper GI bleeding)
      - Octreotide 50 mcg to 100 mcg bolus, then 25 mcg per hour for up to 3 days
    - For EVB (esophageal variceal bleed)
      - 50 mcg bolus, followed by 50 mcg per hr
    - If somatostatin to be used for NVUGIB
      - 250 mcg by bolus, then 250 mcg/hr, for 3 to 7 days

➢ Endoscopic Hemostatic Therapy (EHT)

- Endoscopy
  - Diagnosis
    - Exclude EVB / GVB (esophageal or gastric variceal bleeding
      → If EVB or GVB → EBL (endoscopic band ligation)
      → Prophylactic antibiotics
      → GVB may require "gluing" at time of EGD
- Overall benefit of PPI infusion after EHT, ~ ½ further ↓ in risk of rebleeding, surgery, death
  - Some experts suggest continuing IV PPI infusion in patients bleeding from EV / GV.
- Timing
  - Usually with 24 hrs of index bleed
  - Earlier may be necessary in some patients, such as those presenting with hematemesis or hemodynamic instability.
  - Best done with full GI bleeding term of experience endoscopy nurses, staff, trainees, and available anaesthesiologists and general surgeons

- Adherent clots
  - Gently wash to visualize nature of underlying lesion (allows reclassification of lesion from IIb to IIc, which does not require EHT, or from IIb to IIa, which does need EHT).
- Use two modalities of endoscopic hemostatic treatment, e.g. injection of epinephrine plus thermal coagulation or hemostatic clips
  - Epinephrine 1:10,000 dilution, 0.5 to 2.0 mL aliquots given into 4 quadrants, within 3 mm of bleeding site

Clinical Heads-Ups

Hemospray®, a nanopowder which promotes hemostasis, has been shown in preliminary studies to be > 90% effective in achieving acute hemostasis in persons with ouzing peptic ulcers.

- Second-look EGD
  - No scoring system has been validated to use to predict when rebleeding will occur after endoscopic hemostatic therapy (El munzer et al., 2008).
  - Thus, it is not recommended to routinely undertake a second-look EGD.
  - Unexplained low level of hemoglobin concentration after appropriate transfusion,
  - Unexplained hemodynamic instability, multiple patient morbidities,
  - A high risk bleeding lesion seen at the index of EGD.
  - A planned second-look EGD within 24 hrs of the index EGD may be justified, if there is
    - Poor visualization in the initial EGD
    - Possible poor EHT in the initial EGD
  - An unplanned second-look EGD
    - Persistent or recurrent bleeding

- Interventional Angiography: TAE (transarterial embolization)
  - Success of TAE for index bleed, 52% to 88%
  - Risk of rebleeding, 10% to 20%

- After failed EHT consider TAE for
  - High surgical risk patient
  - Hematobilia or bleeding into pancreatic duct

➢ Surgery in NVUGIB

- Mortality rate
  - Urgent ~25%
  - Elective ~5%
- Recurrent (post-op) bleeding ~5%
- Exclude risks for future rebleeding
  - ASA / NSAIDs
    - Use preventive maintenance co-therapy (PPIs, misoprostil)
  - H. pylori
    - Test and treat, then **must** repeat UBT ± EGD biopsies when off PPI for > 7 days
  - H. pylori-negative, NSAID-negative ulcer
    - Maintenance PPI po, in standard dose, ½ hr before breakfast, maintenance for life

Abbreviations: ABC's, airway breathing circulation; EVB, esophageal variceal bleed; GVB, gastric variceal bleed; UBT, urea breath test (for H. pylori infection); EHT, endoscopic hemostatic therapy

➢ Special circumstance

- Give the clinical features of upper gastrointestinal bleeding in **elderly** versus younger patients.

➢Similarities

- Presenting manifestations of bleeding: hematemesis (50%); melena (30%); hematemesis and melena (20%)
- Peptic ulcer disease most common etiology
- Safety and efficacy of endoscopic therapy

➢ Differences (in elderly patients)

- Fewer antecedent symptoms (abdominal pain, dyspepsia, heartburn)
- More prior aspirin and NSAID use

- More of comorbid conditions
- Higher rates of hospitalization
- Higher rates of rebleeding
- Higher mortality rate

Adapted from: Farrell JJ, and Friedman LS. *Gastroenterol Clin North Am*. 2001;30(2):377-407.

- Give 15 differential diagnoses of bleeding from the upper and from the lower GI tract in persons suffering from **HIV/AIDS**, excluding non-AIDS-related diagnoses.

Infection	Esophagus	Stomach	Small bowel	Colon
Candida	+			
Cytomegalovirus	+	+	+	+
Herpes simplex	+			
Idiopathic ulcer	+			+
Cryptosporidiosis		+	+	
Salmonella sp.			+	+
Entamoeba histolytica				+
Campylbacter				+
Clostridium difficile				+
Shigella sp				+
Kaposi's sarcoma		+	+	+
Lymphoma		+	+	+

Adapted from: Wilcox, C. Mel. *Sleisenger & Fordtran's gastrointestinal and liver disease: Pathophysiology/Diagnosis/Management* 2006: pg. 676.

Clinical Tips

- In the ICU patient on a mechanical ventilator, IV H2-receptor blocker or PPI through the nasogastric tube is superior to sucralfate to reduce stress bleeding (Cook DJ, et al. *N Engl J Med* 1998:791-7; Conrad SA, et al. *Crit Care Med* 2005;33:760-5.

Recurrent Bleeding

- Give 3 **clinical endpoints** which suggest recurrent NVUGIB.
  - If you see blood: NG tube bloody, hematemesis, melena
  - Blood counts ↓ hemoglobin ≥ 2 g/dL after 2 consecutive stable hemoglobins taken 3 hrs apart
  - Vital signs
    - 1 hr of hemodynamic stability: HR ≥ 110 bpm, SB ≤ 90 mm Hg (in the absence of sepsis, cardiogenic shock) or ↑ HR / ↓ SBP within 8 hr post index EGD despite
      - No other explanation e.g. sepsis, cardiogenic shock
      - Continued melena, hematochezia

- Give 15 risk factors for persistent or recurrent gastrointestinal tract bleeding, as well as their approximate odds ratio (OR) for ↑ risk.

Risk Factor	OR
➢ Clinical Factor	
o Age ≥ 70 yr	2.2
o Age > 65	1.3
o Health status (ASA class 1 vs 2-5)	1.9-7.6
o Comorbid illness	1.6-7.6
o Erratic mental status	3.2
o Hypotension (systolic blood pressure < 100 mm Hg)	1.2-3.7
o RF (end-stage renal disease) on dialysis (versus CRF not on dialysis, or non-CRF patients with NVUGIB)	3.8
➢ Presentation of Bleeding	
o Hematemesis	1.2-5.7
o Red blood on rectal examination	3.8
o Melena	1.6
o Transfusion requirement	NA
➢ Laboratory Factors	
o Coagulopathy	2.0
o Initial hemoglobin ≤ 10 g/dL	0.8-3.0

Risk Factor	OR
➢ Endoscopic Factors	
o Diagnosis of gastric or duodenal ulcer	2.7
o GU	
- High on lesser curve	2.8
o DU	
- Superior wall of duodenum	13.9
- Posterior wall of duodenum	9.2
o Active bleeding	2.5-6.5
o High-risk stigma	1.9-4.8
o Clot over ulcer	1.7-1.9
o Ulcer size ≥ 2 cm	2.3-3.5

Printed with permission: Barkun A, Bardou M, Marshall JK. Consensus recommendations for managing patients with non-variceal upper gastrointestinal bleed. *Ann Intern Med* 2003; 139: 843-57, Table 19-5.

- Compare and contrast the endoscopic findings and treatment of portal hypertensive gastropathy (PHG) and gastric antral vascular ectasia (GAVE).

Feature findings	PHG	GAVE
o Site	Fundus	Antrum
o Mosaic pattern	Yes	No
o Red colour signs	Yes	Yes
o Findings on gastric mucosal biopsy		
o Thrombi	No	+++
o Spindle cell proliferation	Sparse	++
o Fibrohyalinosis	No	+++
➢ Management	↓ portal hypertension β adrenergic blockers TIPS Liver transplantation	Estrogens Antrectomy (TIPS doesn't help) Endoscopic laser therapy Liver transplantation

Gastric Varices (GV)

- Primary prophylaxis
  - EGD surveillance 1 to 2 years
  - NSBB
    - Start when
      - ↑ EV size
      - Development of red wales
  - Possibly (one study) cyanoacrylate ("glue") injection for large GV

Outcome	"Glue"	NSBB or placebo
– Probability of first bleed from GV	28%	45%
– Actuarial probability of survival	90%	72%

  - Do not use sclerotherapy, TIPS, shunt of primary prophylaxis of GV.
  - Possibly (one study) cyanoacrylate ("glue") injection for large GV (gastric varices)

– Probability of first bleed from GV	28%	45%
– Actuarial probability of survival	90%	72%

  - Do <u>not</u> use sclerotherapy, TIPS or shunt for primary prophylaxis of GV.
  - EV +GV, treat as for EV; isolated GV, glue or TIPS
  - For acute bleeding GV, or for secondary prophylaxis, "glue" GV with n-butyl-2-cyanoacrylate, or 2-octyl cyanoacrylate
  - TIPS may also be effective for
    - Bleeding GV
    - Secondary prophylaxis
  - Liver transplantation may be considered in selected patients

Abbreviation: TIPS, transjugular intrahepatic portosystemic shunt

NVUGIB plus NSAIDs / ASA

- Useful background
  - Dyspepsia may be associated with the use of NSAIDs, COXIBs, aspirin (ASA)
  - The relative increased risks of ulcer and ulcer bleeding is NSAIDs > COXIBs
  - This risk of bleeding with NSAIDs and COXIBs is increased with
    - The use of
      - ASA
      - Clopidogrel
    - H. pylori infection
  - NSAIDs (excluding naproxen) and COXIBs increase the risk of
    - Hypertension
    - Renal dysfunction
    - Fluid retention
    - Coronary artery disease events
  - Anti-platelet agents
    - Persons with cardiovascular disease (CV) may be on aspirin (ASA) when they develop a NVUGIB.
    - The reflex action may be to stop the ASA to reduce the risk of recurrent ASA-associated bleeding.
    - This is successful from the GI perspective (recurrent bleeding is higher in patients on rather than off ASA, 10.3% vs 5.4%).
    - However, this discontinuation of ASA in the high CV-risk patient leads to a higher CV mortality rate (12.9% vs 1.3%) (Sung et al., Ann. Int. Med.; 2010 152: 1-9).
    - The person with both high CV and GI risk be kept on ASA and that gastroprotective therapy with a PPI be used.

Please see the previous Chapter “Esophageal Variceal Bleeding”

➢ Cotherapy

- Give the recommendations for avoiding peptic ulcers (gastric or duodenal) associated with the use of nonsteroidal anti-inflammatory drugs (NSAIDs) as a function of low, moderate and high gastrointestinal, as well as low and significant cardiovascular risk (CV) (e.g. required use of ASA plus NSAID).

	Low GI Risk	Moderate GI Risk	High GI Risk
○ Low CV Risk (no ASA)	– An NSAID with a low ulcerogenic potential at the lowest effective dose – Consider testing/ treating for H. pylori if starting NSAIDs – Avoid multiple or high dose NSAIDs	▪ NSAID plus PPI ▪ Misoprostol ▪ COXIB	- COXIB plus PPI - Misoprostol
○ Significant CV Risk (requires ASA)	– NSAID plus a PPI	▪ NSAID and a PPI	- Avoid NSAIDs and COXIB, if at all possible

Abbreviations: COXIB, COX-2 inhibitor; CV, cardiovascular risk; NSAIDs, nonsteroidal anti-inflammatory drugs; PPI, proton pump inhibitor.

*these recommendations did not embrace the patients who required antiplatelet therapy, but the same principle is likely to apply.

Printed with permission: Lanza FL, et al. *Am J Gastroenterol* 2009; 104: 728-38.

➢ NSAIDs and gastroprotection

- ○ Concomitant PPI use reduces the risk of development of NSAID-induced endoscopic lesions such as gastric and duodenal ulcers
- ○ Concomitant PPI use is strongly recommended for high risk NSAID users
- ○ PPI co therapy in high risk NSAID users is equivalent to COX-2 therapy in preventing NSID induced endoscopic lesions
- ○ PPI use is effective as secondary prevention of ulcer complications in patients needing antithrombotic therapy with aspirin or clopidogrel

- As an alternative to PPIs, misoprostol can be used in the prevention of NSAID related ulcers and their complications.
- Only high dose famotidine has been shown to reduce DU but not GU in association with the use of NSAIDs.
- PPI co-therapy is effective in the healing and prevention of recurrence of ulcers in patients maintained on longterm NSAID therapy

Adapted from: Arora et al. *Clin Gastroenterol Hepatol* 2009;7: 725-735; Lanza FL, et al. *AM J Gastroenterology* 2009; 104: 734.

- Risk Stratification
  - There are numerous patient-related risk factors associated with the used of NSAIDs, COXIBs, ASA, Clopidogrel. The magnitude of the relative risks should not be compared because various studies were used including different patient populations and risk factors.
  - Treatment algorithms often refer to low, moderate or high gastrointestinal (GI) risk, but actual values of relatives or absolute risk are not used to define these risk categories.
  - It is reasonable to accept that low GI risk comprises a group with no risk factors other than the intake of usual doses of a single agent (NSAID, COXIB, ASA, Clopidogrel).
  - An arbitrary definition of risk stratification for NSAIDs has been provided by Lanza et al. (Am J Gastroenterol 2009; 104: 728-738):
    - High risk
      - History of a previously completed ulcer, especially recent
      - 3 or more risk factors
    - Moderate risk
      - 1 or 2 risk factors
      - > 65 years
      - High dose NSAID therapy
      - A previous history of uncomplicated (non-bleeding) ulcer
      - Concurrent use of any dose of
        - ASA
        - Steroids
        - Anticoagulant

- Give the annual risk for an adverse effect in a 70 year old man on a high dose of NSAIDs, who has a history of a prior bleeding peptic ulcer, and is on maintenance PPI - his H. pylori status unknown (baseline absolute risk, 2.5%).

Risk characteristic			RR
○ Baseline absolute risk for GI event, 2.5%			
○ Increase in risk	-	Age > 65 years	2.5
	-	Use of anticoagulants	2.5
	-	Use of steroids	2.0
	-	History of peptic ulcer disease	5.0
	-	High dose of NSAIDS	2.0
	-	Presence of Helicobacter pylori	1.5
○ Reduction in risk	-	Therapy with proton pump inhibitors	0.5

(2.5 x 5 x 2 x 0.5) 12.5 x 2.5%= 31.3%

Abbreviations: NSAIDs, nonsteroidal anti-inflammatory drugs; PPI, proton pump inhibitor; RR, relative risk.

- COXIBs
  - COX-2 inhibitors are "…probably as effective as a combination of non-selective NSAIDs combined with PPI in patients at risk for ulcers".
  - Considering celecoxib versus diclofenac plus PPI, "….neither treatment could eliminate the risk of recurrent bleeding in very-high-risk patients" (recent history of bleeding peptic ulcer, 6 month risk of ulcer 20% to 25%, risk of recurrent bleeding, 5%.
  - "…..COX-2 inhibitors but also non-selective NSAIDs, with the exception of full-dose naproxen (1000 mg a day), increase cardiovascular risk" (risk ratio for most myocardial infarction, 1.42), and "…….. there was no significant difference in cardiovascular risk between COX-2 inhibitors and non-selective NSAIDs. Naproxen (500 mg twice daily) was the only exception." (Feldman M., et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. *Saunders/Elsevier*, Philadelphia, 2010, page 875).

- H. pylori
  - Eradication of an H. pylori infection ↓risk of
    - Endoscopic ulcer in persons starting on
      - NSAIDs
      - ASA

- Beneficial before starting NSAID therapy
- Ulcer bleeding in persons already on ASA (weak data)
- Mandatory in persons with a history of peptic ulcer disease
- In the patient with NVUGIB associated with H. pylori (Hp) infection start the Hp. treatment as soon as oral feeding is started

- Maintenance therapy with PPIs is "…superior to H. pylori eradication alone in primary or secondary prevention of endoscopic ulcers among NSAID users" (Rostom et al., Aliment Pharmacol Ther 2009; 29: 481-496.

Adapted from Rostom, A. et al., Aliment. Pharmacol. Ther. 2009; 29: 48196.

- H. pylori increases risk of ulcer bleeding ~ 1.8 fold, NSAIDs ~ 4.9-fold, and H. pylori plus NSAIDs ~ 6 fold.
- "Among patients who are about to start NSAID therapy, eradication of H. pylori reduces [by about 50% but does not prevent] the subsequent risk of ulcer development."
- Thus, "…..eradication of H. pylori infection alone is not sufficient for the prevention of ulcer bleeding in NSAID users with high ulcer risk.
- Although H. pylori increases the ulcer risk in patients receiving low-dose aspirin, "co-therapy with PPI after eradication of H. pylori was still required…."

Adapted from: Feldman M., et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. *Saunders/Elsevier*, Philadelphia, 2010, Table 53.2, page 876.

- Anti-platelet drugs
  - Low-dose aspirin alone slightly decreases all-cause mortality (relative risk, 0.93; 95% confidence interval, 0.87-0.99) but increases the risk for major GI bleeding (adds ratio, 1.55; 95% CI, 1.27-1.90).
  - PPI use with aspirin decreases the likelihood of bleeding (OR, 0.34; 95% CI, 0.21-0.57).
  - Low-dose aspirin negates the GI mucosa-sparing effect of COX-2 inhibitor.
  - With combination of ASA with clopidogrel or anticoagulants, the risk for major bleeding is higher than with aspirin alone (OR, 1.86; 95% CI, 1.49-2.31 and OR, 1.93; 95% CI, 1.42-2.61, respectively).
  - Omeprazole can significantly reduce the risk of adverse upper gastrointestinal events in patients receiving clopidogrel alone.

- The patients with acute coronary syndrome or ST elevation myocardial infarction, esomeprazole is superior to famotidine in preventing upper gastrointestinal complications related to aspirin, clopidogrel, and enoxaparin or thrombolytics.

Source: Goldstein JL, et al. Aliment Phamacol Ther 2011; 34: 808; Ng F-H, et al. Am J Gastroenterol 2012; 107: 389-391.

SO YOU WANT TO BE A GASTROENTEROLOGIST!

- In persons who require an NSAID, it is recommended to "use the least ulcergenic NSAIDs at the lowest effective dose"; naproxen 500 mg bid is effective.
- Ibuprofen is available OTC (over-the-counter), and is often advertised as being relatively safe.
- In persons with high GI risk plus high cardiovascular risk (taking ASA), ibuprofen is not recommended, even if PPI co-therapy is used.

- In this clinical scenario, give the reasons why ibuprofen is **not recommended.**

  - Aspirin reduces cardiovascular (CV) risk.
  - In high risk CV patients, ASA must be taken.
  - Ibuprofen reduces the serum concentration of ASA.
  - The lower serum concentration of ASA reduces the CV protection.
  - So, don't combine ibuprofen with ASA in high CV risk patient.

"We are inherently critical as scientists, and inherently kind as physicians."

Grandad

- Useful summary:
  - Odds ratios (ORs) and *P* values for comparisons between gastroprotective strategies for persons using NSAIDs or COXIBs (COX-2 inhibitors).

A. For all upper GI complications.

NSAID + low dose misoprostol (0.74)					
NSAID + PPI (0.67)	0.88 (0.52-1.49) *P* > .20				
NSAID+PPI+low-dose misoprostol 0.58)	0.78 (0.46-1.34) *P* >.20	0.86 (0.47-1.57) *P* > .20			
COXIB (0.51)	0.68 (0.56-0.85) *P* = .0006[a]	0.75 (0.53-1.06) *P* = .11	0.87 (0.52-1.49) *P* >.20		
COXIB + PPI (0.36)	0.48 (0.36-0.65) *P* < .0001 [a]	0.53 (0.36-0.79) *P* =.0018 [a]	0.62 (0.35-1.09) *P* = .093	0.70 (0.55-0.91) *P* = .0068 [a]	
	NSAID+low-dose misoprostol	NSAID + PPI	NSAID + PPI + low-dose misoprostol	COXIB alone	COXIB + PPI
NOTE: Those shown in bold are statistically significant.					

B. For all upper GI complications secondary to peptic ulcer disease.

NSAID + low dose misoprostol (0.61)					
NSAID + PPI (0.50)	0.81 (0.48-1.38) *P* > .20				
COXIB (0.46)	0.74 (0.55-1.00) ***P*** = .050	0.91 (0.55-1.50) *P* > .20			
NSAID+PPI+low-dose misoprostol (l0.29)	0.46 (0.18-1.21) *P* = .117	0.58 (0.21-1.60) *P* > .20	0.63 (0.25-1.60) *P* >.20		
COXIB + PPI (0.23)	0.37 (0.23-0.57) ***P*** < .001[a]	0.49 (0.25-0.82) ***P*** =.0084[a]	0.50 (0.34-0.73) ***P*** < .001[a]	0.79 (0.29-2.09) *P* > .20	
	NSAID + low-dose misoprostol	NSAID + PPI	COXIB alone	NSAID + PPI + low-dose misoprostol	COXIB + PPI
NOTE: ORs for relative risk reduction versus nsNSAID users alone shown in parentheses.					

Printed with permission: Targownik LE, et al. *Gastroenterology* 2008; 134: 937-44.

OBSCURE GI BLEEDING

Useful background: Obscure GI bleeding: Where in the small bowel are the lesions?

- AVM's
  - Jejunum-36%
  - Ileum-34%
  - Jejunum and ileum-30%

- Polyps
  - Jejunum-70% (36% proximal jejunum)
  - Ileum-30% (16% terminal ileum)
  - Endoscopic therapy for AVMs (AV malformations, angiodysplasia, angioectasia, angioma, venous ectasia): less than 10% of persons with angioectasia ever bleed, and 50% will never rebleed.
  - Cessation rates from AVM using push enteroscopy (PE), 57-85% (*AGA technical review, 2007*)
  - One year after double-balloon enteroscopy for AVM, 57% required retransfusion, or are bleeding-free (Gerson LB. *Gastrointest Endosc Clin N Am*. 2009 Jul;19(3):481-96); other studies have shown rebleeding rates ranging from 20-63% (Viazis N, et al. *Gastrointest Endosc*. 2009;69(4):850-6.; Kafes AJ, et al. *Gastrointest Endosc*. 2007;66(2):304-9.; de Leusse A, et al. *Gastroenterology* 2007;132(3):855-6.).

Printed with permission: Feagins LA, and Kane SV. *Am J Gastroenterol* 2009;104:770.

- Diagnostic methods

- Give 10 diagnostic methods for determining the cause of obscure GI bleeding.

  - Endoscopy
    - Capsule endoscopy (CE)
    - Double balloon enteroscopy (DBE)
    - Push enteroscopy (PE)
    - Intraoperative endoscopy
    - Repeat endoscopy
    - Repeat colonoscopy

o Small bowel contrast X-ray	-	Small bowel single contrast
	-	Small bowel double contrast (enteroclysis)
o CT/MRI	-	CT angiography (CTA)
	-	CT/MRI enteroscopy (CTE/MRE)
	-	CT-enterocylsis
o Angiography	-	In the presence or absence of acute bleeding
o Scintigraphy	-	Erythrocyte scintigraphy (RBC scan)
	-	Meckel scintigraphy

Abbreviations: CE, capsule endoscopy; DBE, double balloon enteroscopy; EGD, esophagogastroduodenoscopy; PE, push enteroscopy

Adapted from: Heil U. and Jung M. *Best Pract Res Clin Gastroenterol* 2007;21(3): pg. 402.

A patient has iron deficiency anemia, FOB-positive melena stools, a normal EGD with normal duodenal biopsies (exclude celiac disease), and normal colonoscopy with intubation of the terminal ileum. You are asked to give the "best test" from a long list of diagnostic options for obscure GI bleeding (OGIB), such as:

- Diagnostic imaging
  - Small bowel follow through (barium)
  - Enteroclysis
  - CT or MR enteroscopy
  - RBC scan
  - Meckel scan
  - Angiopathy
- Endoscopy
  - Capsule endoscopy (CE)
  - Push enteroscopy
  - Double balloon enteroscopy
- And the right answer is……..
  - None of these
  - Repeat the EGD / colonoscopy, perhaps by a more experienced operator
  - Most causes of OGIB are identified on the second EGD / colonoscopy

Pros and Cons of diagnostic choices for: Obscure GI bleeding (OGIB)

- EGD / colonoscopy
  - In persons with OGIB, 35-75% of the causes are revealed by second-leak EGD, and 6% by second-leak colonoscopy (Leighton 09). Small bowel lesions account for only 5% of OGIB, and most of these (70%) are vascular lesions (Cellier C. *Best Pract Res Clin Gastroenterol* 2008:329-40).

- Small bowel endoscopy
  - Most of the lesions diagnosed by push enterostomy in persons with OGIB are within the reach of standard EGD.
  - Double balloon enteroscopy (DBE) is superior to single balloon enteroscopy (SBE). DBE can be performed in an oral/antegrade, or anal/ retrograde manner.
  - Approximate depth of endoscopic penetration of small bowel
    - Push enteroscopy 90-150 cm
    - Ileoscopy 50-80 cm
    - DBE,
      - Oral 240-360 cm
      - Rectal 102-140 cm
  - DBE has a diagnostic yield of 60-80% in persons with OGIB suspected to be from the small intestine, with therapeutic intervention being possible in 40-73%.
  - Meta-analysis has shown comparable diagnostic yield for DBE and CE (57-60%), with therapeutic potential with DBE (Pasha SF, et al. *Clin Gastroenterol* Heptaol 2008:671-6.; Chen X, et al. *World J Gastroenterol* 2007;13:4372-8.).

- Capsule endoscopy
  - The diagnostic yield of capsule endoscopy (CE) in the patient with OGIB ranges from 38-83% (Rondonotti E, et al. *World J Gastroenterol* 2007:6140-9).
  - CE is more likely to give a positive yield when there has been more than one episode of bleeding, the bleeding is overt rather than occult (60% vs 46%), CE is performed within 2 weeks of the bleeding episode (91% vs 34%), the bleeding has occurred over more than the 6 months, and the bleeding has resulted in the hemoglobin concentration being < 10 g/dl (Carey EJ, et al. *Am J Gastroenterol* 2007;102:89-95).

- The false negative rate for CE is 19% for tumours, and 11% overall.
- CE cannot be performed in persons with a structure or obstruction, since this would require that the capsule be removed surgically.

- Meckel scan
  - Meckel scan for a Meckel diverticulum is performed with technetium 99 m pertechnetate, and has a sensitivity of 64-100% for bleeding from ectopic gastric mucosa.
  - A false negative Meckel scan may be the result of a recent barium X-ray obscuring the area of uptake, too small a diverticulum, too small a vascular supply to the diverticulum, or too rapid bleeding from the diverticulum washing out the technetium.

- RBC scan
  - The technetium 99 m labeled RBC scan can show slow bleeding, (0.1-0.4 ml/min), whereas angiography needs higher rates of bleeding (>0.5 ml/ min) in order to be positive.
  - With active bleeding, the bleeding site may be localized in 50-75% of patients, but the sensitivity rate falls below 50% with slower rates of bleeding.

- Angiography
  - An angiography suggests angioectasia from a vascular tuft or slow filling of a vein.
  - Therapeutic embolization may be performed with gelfoam or coils.
  - Pipaverine may be infused at the time of angiography.

- CTE
  - For CTE (CT enterography), oral contract is given by mouth and by nasojejeunal tube for CT enterocyclis.
  - The diagnostic yield of CTE in OGIB is 45% (Huprich JE, et al. *Radiology* 2008:562-71.), and may be useful to distinguish fibrostenotic from inflammatory Crohn disease (Paulsen SR, et al. *Radiol Clin North Am* 2007:303-15.; Horsthuis K, et al. *Radiology* 2008:64-79.).

GASTROPARESIS

- Therapy
  - Hormonal therapy use is controversial in persons with bleeding from angiodysplasia, but may be of use in persons with angiodysplastic bleeding and HHT (hereditary hemorrhagic telegangiectasia), van Willebrand disease, or renal failure.

Abbreviations: CE, capsule endoscopy; CTE, CT enterography; DBE, double balloon enteroscopy; HHT, hereditary hemorrhagic telegangiectasia; OGIB, obscure GI bleeding; SBE, single balloon enteroscopy

  - The term "gastroparesis" is used interchangeably with delayed gastric emptying.
  - Usual causes related to impaired motility (gastroparesis) and mechanical obstruction

Gastric Motor Function

  - In order to understand the pathophysiology of gastroparesis, we first need to understand the basics of gastric motor function.

- Autonomic nervous system (ANS)
  - Parasympathetic pathways from
    - DMN (dorsal motor nucleus)
    - NA (nucleus ambiguous)
    - TS (tractus solitarius)
  - Vagus efferents pass to MP (myenteric plexus) in wall of stomach
  - Sympathetic pathways
    - From IML (intermediolateral columns) in T5 to T10 levels of spinal cord from
      - Celiac ganglia to splanchnic efferents
        - Myenteric ganglia — norepinephrine
      - Splanchnic efferents to
        - Submucous ganglia } norepinephrine and somatostatin
        - Circular muscle
        - Blood vessels — norepinephrine and NPY
        - Pyloric sphincter
        - Non-sphincteric muscle

Abbreviation: NPY, neuropeptide Y

- Enteric nervous system (ENS)
  - Main networks
    - SM submucosal
    - Myenteric
    - Deep muscular
      - Interstitial cells of Cajal (ICC)
      - Plexi involved in pacemaking
      - Muscle propulsion (MMC)
        - Sensation
        - Secretion

Abbreviations: MMC (aka IMMC), interdigestive migrating motor complex

- Smooth muscle cells
  - Receptors in the excitable membrane of the smooth muscle cells
  - These receptors bind to amines and peptides which reach the smooth muscle cells from neurocrine, paracrine and endocrine pathways
  - The excitable membrane of the smooth muscle cells fires spontaneously, causing action potentials that cause the muscle cell to contract
  - The muscle cells are joined as a syncytium, which provides electrical coupling of neighbouring muscle cells
  - The contraction resulting from the spontaneous depolarization, action potential and syncytial coupling cause contraction in the circumferential and longitudinal axes.

- Peristaltic reflex
  - Responsible for the “law of the intestine”
  - Ascending contraction: stimulus in the lumen, usually from distention by food
    - Transmitters of excitation of smooth muscle
      - Acetylcholine
      - Serotonin acting on 5HT4 receptors on cholinergic interneurons
      - Tachykinins
        - SP (substance P)
        - SK (substance K)

- Descending contraction: inhibition of smooth muscle below area of stimulation causes descending inhibition
  - Resistance to the movements of the food bolus which is being pulsed distally into the relaxed area by the ascending contraction and the proximal smooth muscle excitation.
  - Transmitters of inhibition of smooth muscle
    - NO (nitric oxide)
    - VIP (vasoactive intestinal peptide)
    - Somatostatin
    - GABA (gamma-aminobutyric acid)
    - Endogenous opiates
  - Pylorus (antroduodenal junction)
    - 0.6 cm to 1.6 cm long, and maintains an area of high resting pressure
    - 3 times per minute phasic contractions sweep across this antroduodenal junction, emptying particles which are 1 mm to 2 mm in size
    - These phasic pyloric contractions are mediatedly NO, Ach and opiates.

- Muscle activity: circular, oblique and longitudinal muscle layers of stomach, which leads to
  - Relaxation of fundus (accommodation)
  - Contraction of antrum (chemical digestion, shearing and pulverization, propulsion, rates pulsion, sieving, emptying of 1 mm to 2 mm particles)

- Give 10 **pathophysiological processes** involved in the **gastroparesis** associated in the diabetes.

➢ Abnormal function of the fundus

- In response to distention of fundus phasic contraction ↓ accommodation due to failure of recovery of ↓ tone of fundus during the fasting (postprandial) period, possible due to a defect in the NO pathway ↓ (50%) of IMMC during fasting associated with antral contraction and the clearance of undigested solids > 1 mm to 2 mm.

- Abnormal function of the antrum
  - ↑ lag time for emptying of stomach
  - ↓ frequency of distal antral contractions (< 1 per minute), causing hypomotility
  - ↑ IPPN (isolated pyloric pressure waves “pylorospams”)
  - ↓ proximal gastric contraction, with failure of food still in stomach to be redistributed, again entering the antrum for trituration and emptying.
  - Abnormal electrical slow wave rhythms, possible from ↑ prostaglandins
    - Brachygastria
    - Tachygastria
    - Mixture of brachygastria and tachygastria
  - Vagal dysfunction, e.g. autonomic neuropathy, hyperglycemia in type 1 diabetes
  - ↓ ICC in deep muscle plexus, e.g. in diabetes possible due to ↓ insulin and IGF-1 → smooth muscle cell produces ↓ stem cell factor
  - ↑ oxidative stress (as in diabetes)
  - ↓ inhibitory nitric oxide containing neurosis
  - ↑ phosphodiesterase -5 activity
  - Associated neuropathic or myopathic abnormalities of small bowel motility

- Causes and associations
  - Ideopathic (36%)
  - Metabolic
    - Diabetes (29%)
    - Thyroid disease
  - GI disorders
    - Previous gastric surgery (13%)
    - Gastric outlet obstruction (mechanical causes)
    - GERD
  - Autoimmune disease
  - Neurological disease
  - Post-viral gastroparesis (may improve spontaneously)

- Drugs
  - Narcotics
  - Anti-cholinergics
  - Diabetic-treating drugs
  - GLP-1
  - Amylin analogs (pramlinitide)
  - Canabinoids
- Eating disorders
  - Rumination syndrome
  - Effortless repetitive regurgitation of recently ingested food into the mouth within 15 min of starting a meal, and followed by rechewing and reswallowing of the food, or spitting out the ruminated food
  - Anorexia nervosa
  - Bulimia
- Cyclic vomiting syndrome
  - Abdominal pain and nausea, sudden onset of vomiting which lasts for several hours over 3-5 days, then followed by vomiting for 3-4 mon

- Diagnosis: best test
  - A gastric emptying study performed with a solid and a liquid test meal will correctly establish whether the gastric emptying was slow at the time of testing.
  - However, there may be a poor correlation between the patient's symptoms, the T1/2 of emptying provided by the emptying study, or their response to prokinetic medications.

- Treatment
  - Treat the underlying condition (e.g. diabetes, medications causing gastroparesis)
  - Complications to be corrected
    - Dehydration
    - Hypokalemia
    - Metabolic alkalosis
    - Hyperglycemia (in a diabetic)
    - Malnutrition
    - GERD

- Nutrition
  - Low fat
  - Low non-digestible fibre
  - Frequent, small meals
  - Liquid meals (including enteral nutrition) po / PEJ (percutaneous endoscopically placed jejunostomy tube)
  - Certain amino acids (e.g. L-tryptophan – [cheese])
  - Avoid offending foods and beverages
  - Vitamin B6 (thiamine) (FDA A)
  - Ginger
  - Soda crackers (popular folklore, but of unproven benefit)
- Treat other factors
  - Rectal/colonic distention
  - Pregnancy
  - Ascites
  - Avoid circular vectoral motion
  - Avoid medications which may relax smooth muscle and thereby aggravate gastroparesis
- Endoscopic therapy
  - PEG (percutaneous endoscopic gastrostomy) and PEG-J (PEG with jejunal extension tube), jejunostomy (surgical, endoscopic, radiographic)
- Gastric electrical stimulation ("humanitarian use device")
  - For diabetic gastroparesis, but not for idiopathic or post-surgical)
- Surgery
  - Decompression
    - Venting gastrostomy
    - Jejunostomy
  - Conversion
    - Previous partial gastrectomy → subtotal gastrectomy or near-total gastrectomy and Roux-en-Y gastrojejunostomy

- "Prokinetics"
  - Metoclopramide
    - Metoclopramide (1% risk of tardive dyskinesia)
  - Domperidone
    - Domperidone (withhold treatment if baseline ECG shows corrected OT > 450 ms (F) to 470 ms (M)
  - Cisapride
    - Metabolized by CYP450 3A4:AEs
    - Antibiotics
      - Macrolide
      - Anti-fungals
      - Phenothiazine
  - Caution
    - Long QT (QTc > 0.45 sec) syndrome → SCD (sudden cardiac death)
  - Erythromycin: 250 mg po tid, as needed, or maintenance
    - Induces high amplitude gastric propulsive contractions
    - Use is limited by tachyphylaxis
  - Azithromycin
    - AEs: ototoxicity
    - Long QT syndrome → SCD
  - Antiemetics
    - Phenothiazines (do not give with cisapride →↑ risk of QTc > 0.45 sec → SCD)
    - Antihistamines
    - 5-HT3 antagonists e.g. ondansetron
    - Trial of TCAs (tricyclic anti-depressants)
  - Botulinum toxin-injection into pylorus
    - Unproven value
- Miscellaneous
  - Acupuncture – "P6" acupuncture point
  - Gastric electrical stimulation

Adapted from: Quigley EMM. *Sleisenger & Fordtran's gastrointestinal and liver disease: Pathophysiology/Diagnosis/Management* 2006: pg. 1007.

- Give the mechanism (s) of action of 8 **prokinetic drugs** which could be used for the treatment of symptoms of gastroparesis.

○ Metoclopramide	– Central/peripheral dopamine receptor antagonist (D_2) – 5-HT3 receptor antagonist – 5-HT4 receptor agonist
○ Domperidone	– Peripheral D_2 antagonist
○ Cisapride	– Muscarinic (acetylcholine) receptor agonist – -5-HT3 receptor antagonist – -5-HT4 receptor agonist
○ Ondansatron	– -5-HT3 receptor antagonist
○ Erythromycin	– Motilin receptor agonist
○ Tegaserod	– Cholinergic 5-HT4 partial agonist
○ Bethanechol	– Muscarinic receptor agonist
○ Anticholinergic (buscopan, for tachygastria)	
○ α-adrenergic antagonists	– α-adrenergic antagonist
○ Botulism toxin injection	– Acetycholine esterase inhibitor
○ Octreotide injection	– Phosphodiesterase inhibitors – Somatostatin receptor agonist

Adapted from: Quigley EMM. *Sleisenger & Fordtran's gastrointestinal and liver disease: Pathophysiology/Diagnosis/Management* 2006: pg. 1007; and 2010, pg. 813.

Clinical Gems:

- Acupuncture may be of benefit for relief of nausea / vomiting (Ezzo JM, et al., Cochrane Database Syst Rev 2006; 2: CD002285.
- Ginger (> 1 g/day) and thiamine (especially for nausea in pregnancy, pyridoxine [Diclectin] 10 mg po bid plus tabs II qhs), are alternates to treat nausea, which have proven benefit.

NAUSEA AND VOMITING

- Definition: A symptom of unpleasant sensation experience prior to vomiting

- Causes of nausea: "N-A-U-S-E-A" (A simple aide de memoire)

N Neurologic CNS, vestibular

A Alcohol and drugs

U Usually accompanies systemic illness

S Stress and psychiatric conditions

E Enteral conditions

Endocrine conditions

A "anticipating" causes

Adapted from: Maclean C. Chapter 55. In: Therapeutic Choices. Grey J, Ed. 6th Edition, Canadian Pharmacists Association: Ottawa, ON, 2011, page 724-734.

- Give the causes and classes of medication used to treat **vomiting**.

Classes of causes	Common disorders	Class of medication
➢ Middle ear	○ Motion sickness ○ Meniere disease	Antihistamines (dimenhydrinate, short acting) – Gravol 50 mg to 100 mg po / pr / IM / IV every 4-6 hour prn (max 400 mg / day) – Benedryl ▪ 25 mg – 0 mg tid qid prn po ▪ 10 mg – 50 mg tid – qid prn po IM / IV – Hydroxyzine ▪ Atarax 25 mg – 100 mg tid – qid prn po / IM Anti-cholinergics Scopolamin patches (Transderm V) 1.5 mg (1 patch) every 72 hr prn

Classes of causes	Common disorders	Class of medication
➢ Gastrointestinal causes	○ Gastroparesis ○ Dyspepsia	Prokinetics (benzamides, dopamine antagonists) – Domperidone 10mg qid po ½ h AC and HS – Metoclopramide 10 mg – 20 mg tid-qid prn po / SC / IV
➢ Stimulation of CTZ	○ CNS conditions ○ Drugs ○ Uremia	Dopamine antagonist Please see above Serotonin antagonists – Ondansetron (Zofran ®) ▪ 4 mg-8 mg od tid po / IV – Granisetron (Kytril ®, Apo-Granisetron) ▪ 1 mg – 2 mg od bid po ▪ 10 mcg / kg IV over 5 min
	○ PONV / DIN / CINV / migraine, vertigo	Phenothiazines – Chlorpromazine ▪ 10 mg – 25 mg every 4 – 6 h prn po ▪ 25 mg – 50 mg every 3-4 h prn IM / IV – Perphenazine ▪ 2 mg – 4 mg every 8 h prn po / IM / IV – Prochlorperazine ▪ 5 mg – 10 mg tid – qid prn po / pr ▪ 5 mg – 10 mg bid / tid prn IM / IV – Promethazine ▪ 12.5 mg – 25 mg every 4-6 h prn po / IM/ IV

Abbreviations: CINV, chemotherapy-induced nausea and vomiting; CTZ, chemoreceptor trigger zone; PONV, post-op nausea and vomiting; DIN, drug-induced nausea

Clinical Pearl: If non-pharmacological approaches fail, and the above approach is also not effective, then combine two or more anti-emetics from different pharmacological classes

- Give the smooth muscle as well as the CNS **receptors** which are responsible for the mechanism (s) of action for 12 drugs used for the treatment of refractory nausea and vomiting.

  - GI receptors
    - Please see previous answer on mechanism of action of prokinetic drugs
  - Central
    - H-1 receptor antagonists (inner ear) – diphenhydramine, promethazine
    - Cannabinoids – dronabinol, nabilone
    - Neurokinin (NK)-1-antagonist – aprepitant, talnetant, osanetant
    - Neuroleptic – chlorpromazine, haloperidol
    - Benzodiazepines
    - 5 HT3 antagonist – Ondansetron
    - Metoclopramide
      - D2 antagonist
      - 5HT3/ 5HT4
    - Tricyclic antidepressants
    - Steroids (e.g. dexamethasone and Mannitol) (nausea and vomiting due to increased intracranial pressure)
  - Gastroparesis
    - The vomiting centre is on the blood side of the blood-brain barrier
    - Some persons with severe, intractable gastroparesis, such as may occur with severe type I diabetes, may improve with near-total gastrectomy and Roux-en-Y anastomosis
    - Slowed gastric emptying and delayed small intestinal transit occur in persons with cirrhosis

"Know yourself.

You are unique, priceless and a gift to the world."

Apoorve Dubey

SO YOU WANT TO BE A CLINICAL PHARMACOLOGIST!

- Give the name of 2 anti-emetics which have been reported to **prolong QTc** and / or PR interval.
  - Butyrophenone
    - Droperidol
  - Serotonin antagonist
    - Delasetron (Anzemet ®)
    - Granisetron (Kytril ®, Apo-granisetron ®)
    - Ondansetron (Zofran ®))
  - Cisapride

- Give the name of 2 anti-emetics for which the dose must be adjusted for
  - Age
    - Droperidol
  - Kidney malfunction
    - Metochlobramine
    - Dolasetron

Adapted from: Maclean C. Chapter 55. In: Therapeutic Choices. Grey J, Ed. 6th Edition, Canadian Pharmacists Association: Ottawa, ON, 2011, page 724-734.

- Give the **drug interactions of the anti-emetics**.

Antiemetic	Other Drug Interaction	Mechanism
➢ ↑ effect of other drugs		
o Antihistamines	- Digoxin	▪ ↑ absorption
o Serotonin antagonists Dolasetron	- Anti-depressant	▪ ↓ CYP 2D6
➢ ↓ effect of other drugs		
o Serotonin antagonists Dolasetron	- Tramadol	

➢ Action of other drugs on effect of anti-emetics

Other drugs	Anti-emetic	Mechanisms
○ Cimetidine	- Serotonin antagonist Dolasetron	– ↑ blood level of active metabolite
○ Rifampin, phenytoin, carbamazeine	- Ondansetron	– ↓ blood level of active metabolite
○ Rifampin	- Dolasetron	– ↓ blood level of active metabolite

➢ **Pregnancy** and **lactation**

- Give the treatment of nausea / vomiting during pregnancy and breastfeeding.

  ○ Dietary and lifestyle modifications
  - Avoidance of precipitating factors
  - Frequent, small meals high in carbohydrate and low in fat
  - Stimulation of P6 acupuncture point
  - Ginger
  - Vitamin B6

  ○ If non-pharmacological measures fail

  ↓

  - Doxylamine 10 mg plus pyridonine (vitamin B6) (Diclectin DR®)) tab 1 bid po plus tabs II qhs

  ↓

  - Dimenhydrinate
    - With no diclectin, 50 mg – 100 mg every 4 -6 h po (Gravol®)
    - With 4 diclectin / day, then dimenhydrinate max 20 mg / day
    - Or promethazine 12.5 mg – 25 mg every 4 -6 h po / pr

  ↓

  - Benzamide (metocloperamide), or
  - Phenothiazine, or
  - Ondansetron (Zofran ®)

*Note: If one treatment fails, move to next step; continue to reassess patient for possible dehydration and need for IV saline and systemic (SC, IM, IV) pharmacological therapy.

Caution: Ensure patient is not pregnant, and in this situation, do not used corticosteroids as an anti-emetic during the first trimester (concern about risk of oral cleft abnormalities)

- Give 4 drugs that may be used for nausea and vomiting in pregnancy and give the FDA pregnancy use category.

Drug	FDA category	Usual dosage
o Domperidone, cisapride	C	1-20 mg tid or qid
o Doxylamine	B	12.5 mg twice daily
o Metoclopramide	B	10-20 mg four times daily (qid)
o Ondansetron	B	4-8 mg tid
o Prochlorperazine	C	5-10 mg tid
o Promethazine	C	12.5-25.0 mg qid
o Vitamin B_6 (thiamine)	A	10-25 mg three times daily

Adapted from: Thukral C, and Wolf JL. *Nat Clin Pract Gastroenterol Hepatol* 2006; 3(5): pg. 258; and Printed with permission: Keller J, et al. *Nat Clin Pract Gastroenterol Hepatol* 2008; 5(8): pg. 433.

Post-operative Nausea and Vomiting

- Give 3 mechanisms for the development of post-operative nausea and vomiting (PONV). Give 5 risk factors and 5 methods to reduce PONV.

➢ Mechanism
  - Release of serotonin from bowel handling stimulates $5HT_3$ receptors on afferent serotonergic pathways that stimulate the brainstem
  - Reduced blood flow to brainstem during surgery
  - Activated cerebral cortical pathways

➢ Risk factors for PONV
  - Post Puberty females
  - Non-smokers
  - Previous PONV
  - Use of volatile anesthetics
  - Intra-operative use of opiates

- High dose neostigmine
- Prolonged surgery
- Intra-abdominal surgery
- Major gynecological surgery

- Methods to reduce the risk of PONV
  - Avoid opioids
  - Avoid nitrous oxide
  - Avoid high-dose reversal agent
  - Adequate hydration
  - High oxygen concentration
  - Propofol anesthetic

Abbreviation: PONV, post-operative nausea & vomiting

Printed with permission: Gan TJ, et al. *Anesth Analg* 2003;97(1):62-71.; and Williams KS. *Surg Clin North Am* 2005;85(6):1229-41.; and adapted from: Kovac AL. *J Clin Anesth* 2006;18(4):304-18.

"A Child's mind is a fire to be kindled, not a vessel to be filled."

Anonymous

GASTRIC TUMORS

Polyps

- Suggestions
  - Biopsy all gastric polyps, as well as intervening non-polypoid gastric mucosa (with hyperplastic polyps, the risk of adenocarcinoma is high in the surrounding normal-appearing mucosal)
  - Treat associated H. pylori infection (especially if polyps are hyperplastic or adenomatous)
  - Resection of polyp
    - Symptoms
    - Evidence of dysplasia on biopsy
  - 1 yr follow-up EGD
    - Adenoma
    - Hyperplastic polyp

- Give 6 causes of **thick gastric folds** seen on an upper GI series or EGD.
  - Folds not actually thickened (eg. barium study is wrong – i.e. suboptimal technique, varices)
  - Malignant Infiltration – adenocarcinoma, lymphoma
  - Benign infiltration -granulomas:e.g.
    - Sarcoidosis
    - TB
    - Crohn disease
    - Severe gastritis (eg. ethanol, H. pylori)
    - Menetrier disease (hyperplasia)
    - Eosinophilic gastritis
  - Multiple gastric polyps (HNPCC, FAP, fundic gland polyps)
  - Hypersecretion (Zollinger-Ellison Syndrome)
  - Fundal varices
  - Worms

Abbreviations: EGD, esophagogastroduodenoscopy; FAP, familial adenomatous polyposis; GI, gastrointestinal; TB, tuberculosis

- Classification
  - Epithelial polyp
    - Fundic gland polyp
    - Hyperplastic polyp
    - Adenomatous polyp
    - Hamartomatous polyp
      - Juvenile polyp
      - Peutz-Jegher syndrome
      - Cowden syndrome
    - Polyposis syndrome (non-hamartomatous)
      - Juvenile polyp
      - Familial adenomatous polyposis
  - Non-mucosal intramural polyps
    - Gastrointestinal stromal tumor (GIST)
    - Leimyoma
    - Inflammatory fibroid polyp
    - Fibroma and fibromyoma
    - Lipoma
    - Ectopic pancreas
    - Neurogenic and vascular tumors
    - Neuroendocrine tumors (carcinoids)

- Give the EGD characteristics and pathological features for 8 types of benign gastric polyps.

Polyp type	Location	Size	EGD	Pathological features
Fundic gland (75%)	Fundus and upper body	<1 cm	- Smooth - Glassy - Transparent - usually multiple	- *Helicobacter pylori*-associated gastritis is rare - Associated with PPI use, may regress - Dysplasia found in patients with associated FAP - Fundic gland polyp: distorted glands - Microcysts lined by parietal and chief cells - No or minimal inflammation

Polyp type	Location	Size	EGD	Pathological features
➢ Hyper-plastic (20%)	○ Random, adjacent to ulcers or stoma sites, or in the cardia if related to acid reflux	Generally <1 cm	○ Small polyps - Smooth dome ○ Large polyps - Lobulated - Erosions	- Atrophic gastritis with intestinal metaplasia - *Helicobacter pylori*-associated gastritis (25%), dysplasia is rare (<3%) and found in polyps <2 cm - *Hyperplastic* elongated, cystic, and distorted foveolar epithelium - Stroma with inflammation, edema, and smooth muscle hyperplasia - Proliferation of surface foveolar cells which line distorted pits that extend into the lamina propria - May also contain parietal, chief and pyloric gland cells - Single antrum, multiple anywhere in stomach and may be associated with Menetrier disease - May be difficult to distinguish from hamartomas or from inflammatory - Associations - H. pylori infection - Atrophic gastritis - Reactive / chemical gastritis when near ▪ Erosion / ulcer ▪ Gastroenterostomy stoma - May be associated with dysplasia or adenocarcinoma - Biopsy around hyperplastic polyp to detect high risk of adenocarcinoma in normal appearing mucosa
➢ Adenoma	○ *Incisura angulari* ○ Antrum and fundus	<2 cm	- Velvety, lobular surface - Exophytic - Sessile or pedunculated - Usually solitary (82%)	- Common in antrum - Associated with atrophic gastritis and intestinal metaplasia - Not associated with H. pylori - Neoplastic progression ▪ Tubular, 5% ▪ Villous, 30% ▪ > 2 cm diameter ▪ ↑ age - May be accompanied by coexistent carcinoma - *Adenoma* ▪ *D*ysplastic intestinal- or gastric-type epithelium with variable architecture

Polyp type	Location	Size	EGD	Pathological features
➢ Inflam-matory fibroid	○ Submuco-sal ○ Near the pyloric sphincter	Median 1.5 cm; generally <3 cm	○ Single ○ Firm ○ Sessile ○ Well-circumscribe ○ Ulceration is common	- Pernicious anemia commonly found (atrophic gastritis) - Genetic mutations are common - CD34+ spindled stromal cells - Inflammatory cells - Thin-walled vessels in a myxoid stroma - Pathology ▪ Not "inflammatory" ▪ Well circumscribed, submucosal lesions, smooth surface of normal mucosa ▪ CD34 and fascin positive spindle cells and eosinophils surrounding blood vessels ▪ Usually in antrum ▪ Females > 50 yr ▪ No malignant potential
➢ Peutz-Jeghers	○ Random	<1 cm	- Pedunculated - Velvety or papillary surface	- Risk of adenocarcinoma rare in gastric polyps - Mucocutaneous pigmentation of buccal mucosa, lips, fingers - Hyperplastic glands in stomach lined by foveolar epithelium and broad / branching bands of smooth muscle - ↑ GI / non-GI cancer ▪ De novo ▪ Sequence of hamartoma-adenoma-Ca - Screening breast, uterus, lung, pancreas ▪ EGD q 2 yr after 18 yr ▪ Biopsy > 5 polyps ▪ Remove polyps > 1 cm

Polyp type	Location	Size	EGD	Pathological features
➢ Juvenile	○ More in the body than antrum	Variable	○ Rounded ○ Superficial erosions ○ Multiple	- Polyps may exclusively involve stomach - Lifetime risk of adenocarcinoma > 50%; but - Rare in gastric polyps - Irregular cysts lined by normal gastric epithelium - Associated chronic inflammation, ulceration, bleeding - Follow-up EGD q 3 yr after age 18 - Gastric adenocarcinoma develops > 50% - Glands ▪ Long ▪ Tortous ▪ Cystic dilation ▪ Overlying mucosa - Gastritis - Edema - Bleeding
➢ Xanthoma	○ Antrum ○ Lesser curvature ○ Prepyloric	< 3 mm	○ Multiple in groups ○ Sessile ○ Pale-yellow nodule or plaque	- Chronic gastritis - No association with hyperlipidemia - Aggregates of lipid-laden macrophages in the lamina propria
➢ Pancreatic heterotopias	○ Antrum ○ Prepyloric	0.2-4.0 cm	○ Solitary ○ Dome-shaped ○ Central dimple ○ Smooth surface	- Very rare instances of associated pancreatitis, islet-cell tumours, adenocarcinoma - *Pancreatic heteropia* ▪ Normal components of pancreatic parenchyma
➢ Gastro-intestinal stromal tumour (GIST)	○ Sub-mucosal	Variable (median 6 cm)	- Well-circumscribed - Overlying mucosa may be ulcerated	- 25% are malignant; risk of aggressive behaviour depends on size and mitotic count - CD117+, CD34+ spindle cell or epitheliod cell tumour with variable pattern, mitoses, and stroma

Polyp type	Location	Size	EGD	Pathological features
➢ Carcinoid (NET)	○ Body ○ Ffundus	<2 cm, larger if sporadic	○ Firm ○ Yellow ○ Broad-based ○ Multiple ○ Sporadic lesions: large and single	- Autoimmune ▪ Atrophic gastritis with intestinal metaplasia ▪ Parietal cell hyperplasia in ZES ▪ Normal mucosa if lesion is sporadic - Associated with hypergastrinemia, autoimmune atrophic gastritis, ZES or MEN - *Carcinoid* ▪ Nodular proliferation of neuroendocrine cells >500 µm in diameter - ECL-cells staining positive by immunohistochemistry for chromogranin A, or synaptophysin - Type I (80%) ▪ Sessile ▪ Associated with atropic gastritis, achlorhydria and antral G cell hyperplasia ▪ Good prognosis ▪ Remove large type I gastric NET - Type 2 (5%) ▪ MEN1, ZE (Zollinger-Ellisson) syndrome (ZES) ▪ Treat ZES - Type 3 (15%) ▪ Sporatic ▪ No hypergastrinemia ▪ Poor prognosis

Abbreviations: EGD, esophagogastroduodenoscopy; FAP, familial adenomatous polyposis; MEN, multiple endocrine neoplasia; NET, neuroendocrine tumor; ZES, Zollinger-Ellison syndrome

Adapted from: Carmack SW, et al. *Am J Gastroenterol* 2009;104(6): 524-532.; and Carmack SW, et al. *Nat Rev Gastroenterol Hepatol* 2009;6(6): 331-341.

Fundic Gland Polyps

- Definition

The term fundic gland polyp" needs to be understood in its context: when the endoscopist reports fundic gland polyps, strictly speaking this means that there are polyps in the fundus or fundic gland area of the stomach.

However, the term "fundic gland polyps" implies a specific type of polyps in the fundus.

  - Oxyntic gland mucosa – cystic dilation
  - Other gastric cells (parietal, - decreased chief, mucous neck cells)

- Types

There are two types of fundic gland polyposis, these which are sporatic or familial.

- Give the features which distinguish between sporatic versus familial fundic gland polyposis, as defined by the above histopathology.

Feature	Sporatic	Familial
Associated with mutations in		
- Beta-catenin gene	+	-
- APC gene (chromosome)	-	+
- Dysplasia	3%	25%

  - Familial polyposis syndrome affecting stomach
    - Autosomal dominant germline mutation in APC gene on chromosome 5q21
    - Gastric polyps occur in ~30% of FAP, mostly
      - With no diclectin, 50 mg – 10FGP (fundic gland polyps, 95%)
      - Adenoma of stomach (5%) and duodenum
    - EGD q 1-2 yr with age 50, then EGD q 5 yr
  - Juvenile polyposis
    - Mutations in BMPRIA, 10q22.3, SMAD4, 18q21.1

- Progression to dysplasia and cancer
  - Fundic gland polyp (FGP) (~ 50%)
    - FGP > 1 cm, progression to GCa ~ 1% per year
    - FGP in familial adenomatous polyposis, dysplasia in 40%
  - Adenomas (10%)
    - Progress to GCa (in situ), 11% in 4 years
  - Ménétrier's disease
    - Progress to GCa in 15%
  - Previous partial gastrectomy
    - Especially Billroth II
    - Low risk of development of stromal (marginal) ulcer > 25 yr after surgery
  - Hyperplastic
    - Rare progression to GCa

Premalignant Conditions

- Persons with gastric cancer (GCa) have a 5 year survival rate of only about 25%.
- H. pylori infection is a premalignant condition, and treatment of this infection either early in life (before "point of no return") or in persons who have had EMR (endoscopic mucosal resection) for early gastric cancer may reduce the risk of development or redevelopment of GCa.

- Give 7 other **premalignant conditions** for GCa.

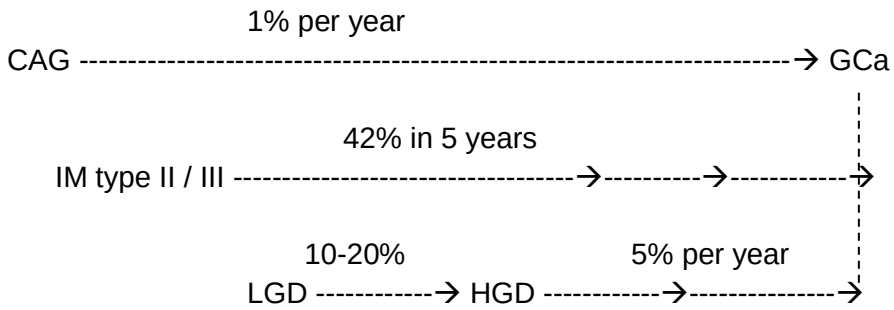
  - Chronic atrophic gastritis (CAG)
    - Risk of progression of chronic atrophic gastritis to GCa
    - Commonest cause of CAG is H. pylori infection (accelerates progression of CAG → GCa)

    1% per year

    - Depends on the extend of CAG
    - MAG >> corporal atrophic gastritis risk

- Production of pepsinogens (PG) from oxyntic cells
  - ↓ PGI
  - PG II, normal
  - ↓ PG I / PG II
- Intestinal metaplasia (IM)
  - Type I
    - Complete metaplasia
      - Absorptive cells with BBM (brush border membrane)
      - Paneth cells
      - Goblet cells (sialomucins)
  - Type II
    - Incomplete
      - Goblet cells
  - Type III
    - Intermediate
  - Risk of early gastric cancer (GCa) in type II / III interstitial metaplasia, 42% in 5 years
- Dysplasia
  - LGD (low grade dysplasia)
    - Regresses in 60%
    - Progresses to HGD (high grade dysplasia) in 10% to 20%
  - HGD
    - Progresses to GCa in 5% per year

- Progression of stages of chronic active gastritis (CAG) to gastric adenocarcinoma (GCa)



Abbreviations: GCa, gastric cancer; IM, intestinal metaplasia; LGD, low grade dysplasia; HGD, high grade dysplasia

- For premalignant lesions on biopsy, give the approximate annual risk of developing gastric cancer (GC).

Pathology	Annual risk	Recommended EGD/biopsy follow-up
○ Atrophic gastritis (AG)	– 0.1%	▪ None
○ Intestinal metaplasia (IM)	– 0.25%	▪ 2-3 years
○ Mild to moderate dysplasia (MMD)	– 0.6%	▪ 1 year
○ Severe dysplasia (SD)	– 6.0%	▪ Endoscopic mucosal resection

Abbreviation: EGD, esophagogastroduodenoscopy ; EMR, endoscopic mucosal resection

Adapted from: De Vries AC, et al. *Gastroenterology* 2008;134:945-52.

➢ Diagnosis

- ○ Patients with new onset dyspepsia plus alarm symptoms ar any age, or new-onset dyspepsia at age ≥ 50 to 55 yrs must have an EGD
- ○ At least 6 mucosal biopsies must be taken from the edge of any gastric ulcer, or any suspicious gastric mass lesion or stricture
- ○ Staging is performed with
  - CT multiplanar of chest, abdomen and pelvis
  - EUS (endoscopic ultrasound)
  - PET-CT scanning should be used in combination with EUS and CT for esophageal and for esophageal-gastric junctional tumor assessment
- ○ Diagnosis of high grade dysplasia should be made and confirmed by "… two histopathologists, one with special interest in gastrointestinal disease"

Early EGCa

➢ Definition of EGC: Gastric cancer which is T1 and N (EGCa is gastric cancer which invades no more deeply into the submucosal, regardless of the involvement of lymph nodes).

- Synchronous and metachronous EGC

	Synchronous EGCa (second EGCa within 1 year)	Metachronous EGCa
o EMR	9.2%	8.2%
o Partial gastrectomy	-	2% to 8%

- EGCa with lymph node involvement
  - Mucosal EGC 2% to 3%
  - Submucosal EGC 20% to 30%

- Give the importance of the number of perigastric lymph nodes on the longterm survival from EGCa.

# of nodes	Longterm survival
0	92-95%
1 to 3	82-88%
4 to 6	73%
> 6	27%

- Management of EGCa
  - Staging of EUS (endoscopic ultrasound)
  - Test-and-treat for associated H. pylori infection
    - Because H. pylori load falls with development of EGCa, biopsies may be falsely negative
    - Treat for H. pylori infection based on positive serology
    - Treating H. pylori infection in EGCa managed by EMR decreases tumor recurrence at 3-years (OR 0.35)
  - Adjuvant therapy for EGCa with positive nodes and observation for TINO
  - Endoscopic mucosal resection (EMR)

- EMR (endoscopic mucosal resection)
  - Successful EMR ~85%
  - Lower success rates with EGCa > 2 cm

- Ulcerated
- Undifferentiated)
- 5 year survival rates ~86%
- For incomplete resections
  - Repeat EMR
  - Laser irradiation
  - Heater probe cautery
  - Surgical resection
- If positive lateral margins and negative vertical margins
  - No submucosal or lymphovascular invasion
- Piecemeal resection ↑ risk of recurrence (28%)

➢ ESD (endoscopic submucosal dissection)

- ESD complete resection > EMR (83% vs 24%)
- If positive vertical or lateral resection margins after ESD → gastrectomy
  - Laparoscopic versus open distal gastrectomy give similar outcomes
- Operative morbidity 22%
  - Operative mortality 0%
  - 5 year survival 96%
  - Disease-specific survival 98%

- Give the **criteria for endoscopic mucosal resection** (EMR) of intestinal type EGCa.
  - High probability of en bloc resection
  - Tumor history
    - Intestinal type adenocarcinoma
    - Tumor confined to the mucosa
    - Absence of venous or lymphatic invasion
  - Tumor size and morphology
    - < 20 mm in diameter, without ulceration
    - < 10 mm in diameter, if Paris classification IIb or IIc

- Expanded criteria
  - Mucosal tumor, any size without ulceration
  - Mucosal tumor < 30 mm with ulceration
  - Submucosal tumors, < 30 mm confined to the upper 0.5 mm of the submucosal, without lymphovascular invasion
- If criteria for EMR are not met → gastrectomy and removal of perigastric lymph nodes to ↓ risk of lymph node metastases
- Type of surgery is determined by site of EGCa
  - Upper 1/3 total gastrectomy
  - Lower 2/3 subtotal gastrectomy

➢ Other treatment options for EGCa

- PDT (photodynamic therapy)
  - Photofrin II plus argon laser
  - Tissue-destroying – cannot examine tissue to determine if margins are clear
- Surgery:
- General indications for **gastrectomy,** with removal of perigastric lymph nodes
  - Low probability of en bloc resection with EMR (endoscopic mucosal resection of mucosa) or ESD (i.e., endoscopic submucosal dissection, the endoscopic resection would be piecemeal)
  - Diffuse rather than intestinal type adenocarcinoma
  - Submucosal tumor size greater than 30 mm, or tumors with ulceration
  - Evidence of lymphovascular (lymphatic or venous) invasion in the primary tumor, or known/suspected regional lymph node metastases
  - Gastrectomy with resection of perigastric regional nodes
    - EGCa with positive lateral or vertical margins
  - Laparoscopic lymph node dissection not yet ready for “prime time”
  - 5 year survival rate for EGCa treated with gastrectomy ~98%

From D. Mogan Up To Date, “Early gastric cancer: Treatment, natural history and prognosis”.

- Give the four generally accepted criteria for endoscopic mucosal resection (EMR), in certain early gastric cancer (EGCa).

  There are (Feldman M., et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. *Saunders/Elsevier*, Philadelphia, 2010, page 902).

  - "the [gastric} cancer is located in the mucosa and the lymph nodes are not included, as indicated by EUS"
  - There is no ulcer scar and the maximum size of the tumor is
    - Type IIa less than 2 cm when the lesion is slightly elevated
    - Type IIb or IIc, less than 1 cm when the tumor is flat (b) or slightly depressed (c)
  - There is no evidence of
    - Multiple gastric cancers, or
    - Simultaneous abdominal cancers
  - "The cancer is of the intestinal type" (i.e., not the diffuse type)

Feldman M., et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. *Saunders/Elsevier*, Philadelphia, 2010, page 903.

"Use diagnostic imaging to guide your clinical impression, not to make the diagnosis."

Dr. Joel Hurwitz

Advanced GCa

- Classification of Macroscopic types of gastric cancer

Type	Japanese classification	Paris classification
0	Superficial, flat tumours with or without minimal elevation or depression	Superficial polypoid, flat/depressed, or excavated tumours
0I	Protruded 	Polypoid
0IIa	Superficial and elevated 	Non-polypoid and nonexcavated, slightly elevated
0IIb	Flat	Non-polypoid and nonexcavated, completely flat
0IIc	Superficial and depressed 	Non-polypoid and nonexcavated, slightly depressed without ulcer
0III	Excavated 	Nonpolypoid with a frank ulcer
1	Polypoid tumours that are sharply demarcated from the surrounding mucosa and are usually attached on a wide base	Polypoid carcinomas that are usually attached on a wide base
2	Ulcerated carcinomas that have sharply demarcated and raised margins	Ulcerated carcinomas that have sharply demarcated and raised margins
3	Ulcerated carcinomas that have no definite limits and infiltrate into the surrounding wall	Ulcerated, infiltrating carcinomas that have no definite limits
4	Diffusely infiltrating carcinomas in which ulceration is not usually a marked feature	Nonulcerated, diffusely infiltrating carcinomas
5	Carcinomas that cannot be classified into any of the above types	Unclassifiable advanced carcinomas

- According to Japanese classification of gastric carcinoma, for the combined superficial types, the type occupying the largest area should be described first, followed by the next type (e.g. IIc+III).
- Types 0 I and 0 IIa are distinguished from each other by lesion thickness: type 0 I lesions have thickness more than twice that of the normal mucosa and type 0 IIa lesions have a thickness up to twice that of the normal mucosa.
- Modified from data presented in the Japanese classification of gastric carcinoma and the Paris endoscopic classification of superficial neoplastic lesions.

Printed with permission: Yamamoto H. *Nat Clin Pract Gastroenterol Hepatol* 2007;4(9): pg. 513.

- In the context of gastric cancer, give the meaning of Virchow node, Sister Mary Joseph Node, Krukenberg tumor and Blumer shelf.
  - Virchow node
    - Supraclavicular lymphadenopathy, left side
  - Sister Mary Joseph node
    - Periumbilical node
  - Krukenberg tumor
    - Enlarge ovary from metastatic gastric cancer
  - Blumer shelf
    - Palpation of rectal mass in the cul-de-sac from metastatic gastric cancer

➢ Causes, associations, and risk factors

- Give **8 risk factors** associated with the development of gastric adenocarcinoma.
  - Genetic--First degree relative with gastric cancer (hereditary diffuse gastric cancer; 2-3 fold increased risk with mutations in E-cadherin CDH1 gene)
  - Polyps
    - HNPCC >> FAP)
    - Peutz-Jeghers syndrome (PJS)
    - Hamartomas
    - Menetrier syndrome

- Chronic atrophic gastritis *(CAG)--H.pylori* infection, pernicious anemia, chronic atrophic gastritis, subtotal surgical resection with vagotomy (for benign gastric ulcer disease)
- Intestinal metaplasia dysplasia
- Diet-- salted, pickled or smoked foods, low intake of fruits and vegetables
- Life style--Smoking (EtOH is not an independent risk factor)
- Barrett esophagus (cancer of cardia)

Abbreviation: HNPCC, hereditary nonpolyposis colon cancer; FAP, familial adenomatous polyposis

Adapted from: Houghton JM and Wang TC. *Sleisenger & Fordtran's Gastrointestinal and Liver Disease: Pathophysiology/ Diagnosis/ Management* 2006*:* pg 1149.

➢ Treatment

- Surgery
  - Resection of spleen and splenic hilar nodes for proximal gastric tumors on greater curve / posterior wall
  - Gastric resection
    - Antrum
      - Subtotal gastrectomy, plus
      - Distal pancreatic resection for direct immersion form proximal stomach
    - Body
      - Total gastrectomy
    - Cardia, subcardia, EGJ
      - Transhiatal extended total gastrectomy, or
      - Esophagogastrectomy
    - Lymph nodes
      - D2 lymphadenectomy for gastric cancers stage II or III

- Chemoradiatiotherapy
  - Pre- / post-operative combination chemotherapy
  - Adjuvant chemotherapy if neoadjuvant chemos' not given to patient with high risk of recurrence

- "Chemotherapy for locally advanced gastric cancer without distant metastasis can result in shriking of the tumor to the point at which successful curative resection is possible.
- "Combined chemoradiation after surgical resection appears to be effective at improving progression-free and overall surgical in gastric cancer."
- After surgical resection for cure of GCa, if there are potential metastasis, intraperitoneal but not systemic chemotherapy may be useful.
- Post-operative hyperthermic intraperitoneal chemotherapy improves overall survival, as compared with just surgery.

Feldman M., et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. *Saunders/Elsevier*, Philadelphia, 2010, page 904.

- Palliation
  - Limited resection
  - Palliative combination chemotherapy
    - Trastuzumab plus cisplatin / fluoropyrimidine for HER2 positive tumors
    - Irinotecan for second-line chemotherapy in patients with good performance characteristics

Source: Allum et al; Gut 2011; 60: 1449-1472.

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GASTROINTESTINAL STROMAL [MESENCHYMAL] TUMORS GIST

- Pathology
  - Site
    - Stomach (fundus) ~70%
    - Small bowel ~25%
    - Colon / rectum 5%
  - Malignant potential
    - All GISTs > 10 mm
  - Leiomyosarcomas
    - Advacent structures
      - No invasion — local resection (lymph node metastases are rare, so usually don't need a nodal resection), with TFM (tumor-free margins)
      - Invasion — en bloc segmental resection, with TFM
  - Survival rates
    - 3 years 53%
    - 5 years 22%

- Genetics (genetic mutations)
  - Mutational activation of genes (proto-oncogenes)
  - Kit
  - PDGFRA
  - CD117 antigen positive (intestinal cells of Cajal), 80%
  - Spindle cell CD117 antigen negative tumors

- Give the **genetics of GIST tumors** which provides the rationale for the use of imatinib for advanced (metastatic / inoperable) disease.
  - CD117
    - Positive (80%)
    - Activation mutation of the KIT proto oncogene → ↑ KIT expression
    - KIT is part of the c-kit receptor, a membrane TK (tyrosine kinase)
    - CD117 is part of the KIT (c-kit) receptor
    - Activation leads to tumor growth

- CD117 mutation in the TK of GIST tumors is associated with response to imatinib.
- CD117 negative (20%), PDGFRA-positive
  - Activation mutation in another TK receptor, PDGFRA (platelet-derived growth factor receptor alpha)
  - Activation leads to tumor growth ~66% of PDGFRA-positive GISTS are imatinib-resistant

➢ Diagnosis

- EUS plus FNA
- Markers for GIST / Immunohistochemical (IHC) studies

- Give the ways to distinguish GIST from leimyomas (LM) and from leimyosarcomas (LMS).
  - C-kit (a stem cell factor receptor) (~99%)
    - CD34 (a hematopoietic cell progenitor cell antigen) (70%)
    - Smooth muscle actin (20% to 30%)
    - S 100 protein (marker of neural differentiation)

IHC antibody	GIST	LM / LMS
C-kit (CD117)	+	-
Smooth muscle actin	-	+
Desmin	-	+

Note: EUS / FNA rather than IHC will differentiate between leiomyoma and leiomyosarcoma

- Give 4 examples of CD117 negative GI spindle tumors (20%).

Fat	– Lipoma
Muscle	– Leiomyomas – Leimyosarcoma
Blood vessels	– Hemangiomas
Nerve tissue	– Schawannomas

- Note: Rarely these above tumors may be CD117 positive, but despite this the non-GIST soft tissue sarcomas do not respond to imatinib

➢ Is a GIST benign or malignant?

- Several risk stratification models (e.g. NIH, AJCC, UICC, AFIP) for discrete categories, continuous variables, or prognostic contour maps or risk of disease recurrence after complete surgical resection (e.g. tumor nomogram).
- General concept: adverse prognostic factors and predictive of high-risk for GIST recurrence, and likely benefit from TKI adjuvant therapy
  - Size ≥ 5 cm, or ≥ 10 cm

	Number < 5
- Mitotic count	> 5 mitoses / hpf
- Mitotic rate	> 10 / 50 hpf (> 1/5 hpf)

➢ Treatment

- Surgery

➢ Assessment of surgical resectability

- Choi Criteria for response to imatinib assessed on contrast-enhanced CT scans depend on size and change in tumor density on dual PET/CT scanning
  - ↓ 10% in tumor size
  - ↓ 15% in tumor density
  - Choi criteria are better predictor of tumor response than RECIST (response evaluation criteria in solid tumor)
- Segmental resection for ≥ 2 cm; leaving the tumor pseudocapsule intact
- Obtain negative tumor resection margins
- Laroscopic resection is possible
- Neoadjuvant therapy with imatinib GISTs ≥ 3 cm
  ↓ GIST recurrence in post-op year 1
- Treatment of advanced disease, and palliation

- Pharmacological
  - TKIs control GIST tumor growth in ~80%
    - Use neoadjuvant TKIs for 6 months, with imaging and reassessment for consideration if possible suitable for resection surgery
  - The use of tyrosine kinase inhibitors (TKIs), eg. imatinib 400 mg to 800 mg/day, depends on GIST mutation

Mutations	Most Common Site of GiST	Response	Dose per day	Time (months) to disease progression
- Exon 11	Stomach	72%	400 mg	25
- Exon 9	Small bowel	44%	800 mg	17
- None		45%	400 mg	13

  - TK (tyrosine kinase) inhibitors for GIST include imatimib and sunitinib
  - TKIs for
    - Unresectable or metastatic disease
    - Adjuvant therapy and surgery
  - Stable tumor is as good as responsive tumor, i.e. response to imatinib is the absence of tumor progression after 3 months therapy.
  - ↓ size of tumor in several days, but tumor may then enlarge from bleeding into the tumor or myxoid degeneration (interpretation: early ↑ size of tumor after imatinib does not necessarily mean failed therapy)
  - Difficult to determine if tumor is progressing of criteria are only tumor size, since a tumor may become cystic and appear to be stable, but new growth occurs in the cystic area ("nodule-within-a-mass") (hypodense cystic lesion becoming filled with hyperdense new tumor, used in Choi but not in RECIST criteria because of inclusion of density characteristics.
  - Surgical resection
    - Size
      - 1 cm, resect if EUS shows
        - Irregular borders
        - Cysts
        - Ulceration
        - Echogenic foci
        - Heterogeneity (lack of homogeneity suggests area of necrosis)
      - 2 cm, resect
    - > 2 mitoses per 10 hpfs (high power field)
    - ~50% recurrence within 5 years

- Tyrosine kinase inhibitors (TKIs)
  - Inhibition of receptor TKs results in ↓ growth of tumor
    - TK receptor antagonists bind to an ATP-binding site in TK receptors
    - Binding to TK receptors → ↓ phosphorylation of TK receptor
    - ↓ phosphorylation of TK receptor → ↓ activation
    - ↓ activation mutation of TK receptor → ↓ tumor growth
    - All KIT mutations are responsible to imatinib, whereas only some PDGFRA mutants are sensitive to imatinib
    - Some non-genetic inhibitory effects of TK receptor inhibitors may result from an anti-GIST immune response
  - Dose
    - Mostly small bowel GISTs require higher dose of imatinib when EXON and KIT positive
    - Exon and KIT positive
      - HR 0.58 for PFS for 800 mg vs 400 mg daily dose (i.e., use 800 mg imatinib)
    - Exon and KIT negative
      - RFS 800 mg = 400 mg
      - Do not require higher dose (i.e., use 400 mg imatinib dose)

Abbreviation: RFS, recurrence-free survival

  - Trough level
    - Trough level of imatinib correlates with better clinical outcome.
    - Keep trough level > 1100 ng/mL
    - Factors which may be associated with low trough levels, and therefore a higher imatinib dose will be benefitial
      - Gastrectomy
      - ↑ serum albumin concentration
      - ↑ CCr (creatinine clearance, leading to ↓ trough concentrations of imatinib
      - Longer durations of treatment with imatinib
  - After ~ 2 years of TKI therapy, tumor develops new KIT mutations, and
    - Tumor may grow
    - Options
      - Continue imatinib
      - Switch from imatinib to sunitinib
      - Resection of residual disease, while continuing TKI to prolong survival

- Metastatic disease
  - Limited progression
    - Continue TKIs, plus surgery
  - Generalized progression
    - TKIs
- Liver metastases
  - Isolated
    - Hepatic resection plus TKI for non-multifocal bilobar disease (resectable disease)
  - For non-resectable (multi-focal bilobar disease)
    - Hepatic arterial embolization with or without TCI (imatinib or sunitinib [a multi-targeted TKI for imatunib-resistant disease])

- Give the **mechanism for the loss of imatinib responsive** in CD117-positive GIST tumors over time (> 1 yr; secondary resistance).
  - Over time there may be an increase in the renal clearance of imatinib, leading to ↓ trough levels
  - ↓ trough levels of imatinib → ↓ responsiveness of the tumor to the inhibition of the TK kinases (C119 and PDGFRA)
  - Rate of tumor recurrence
    - Approximate 50% 5 year RFS (recurrence free survival)
    - Scoring system to fine-tune risk of recurrence
  - Although GIST tumor with PDGFRA EXON 18 D842V may recur, it is not sensitive to imatinib

- Give the reason why **PDGFRA-positive** (and therefore CD-117-negative) mutant patients with a GIST tumor may still be offered imatinib.
  - While 2/3 of PDGFRA mutants are imatinib-resistant (D842V substitution), 1/3 of PDGFRA mutants are imatinib-sensitive.
  - Unless genetic testing can be done looking for the D842V substitution, the PDGFRA patients still should to be treated because of this 1 in 3 chance of responding to imatinib

- Duration of treatment
  - Do not stop imatinib therapy after tumor has progressed
  - Tumor suppression with imatinib must be maintained
  - Stopping imatinib after an initial response only leads to return of progression of tumor.
  - The maintenance TKI must not be stopped, for fear of recurrence of GIST
  - Continued (maintenance) TKI Rx for at least 3 years is necessary even after successful surgical resection of the GIST.
  - Non-regression or local progression of GIST on imatinib is not a bad outcome as long as the tumor does not progress (i.e. stable disease is not necessarily bad) to become generalized disease
  - Generalized GIST progression while patient is on TKI has little to offer, and may be discontinued.
  - Sometimes it is necessary to temporarily stop treatment with imatinib because of the AEs (adverse effects)
  - These AEs may improve even with the continuation of therapy

- Give 4 indications for **imatinib** neoadjuvant therapy prior to resection of a GIST.
  - Unsectable / borderline resectable locally advanced GIST
  - Potentially resectable locally advanced GIST, with extensive organ distruction
  - Source of GIST
    - Esophagus
    - EG (esophagogastric junction)
    - Duodenum
    - Distal rectum

- Give 8 **adverse effects** of imatinib.
  - Skin
    - Periorbital edema
    - Rash

- MSK
  - Muscle cramps
- GI
  - Nausea, vomiting, dyspepsia
  - Diarrhea
- Hematology
  - Anemia
  - Thrombocytopenia
  - Macrocytosis
  - Neutropenia
- Kidney
  - Hypophosphatemia
- Endocrine
  - Gynecomatia
- Heart
  - Low risk of heart failure (HF) in patients with pre-existing heart disease

SO YOU WANT TO BE A GASTROENTEROLOGIST!

Neoadjvant therapy for GIST with imatinib (starting TKI 6 months before surgical resection), with imaging diagnostic studies to assess response and for timing of resection is a useful approach. The median time to best response is 3.5 months, and further shrinkage is uncommon after 9 months of TKI.

- Give the findings on DI (diagnostic imaging) which suggest that the GIST is responding to imatinib.

  - An optimal response to imatinib is
    - Development of cystic structures
    - Change in vascularity
  - Change in tumor size are less important

Sunitinib

- Alternate to imatinib
- Switch from imatinib to sunitinib for
  - Life-threatening side effects (intolerant) to imatinib
  - Imatinib-refractory condition (secondary resistance)
- Secondary resistance to imatinib may occur from
  - Secondary mutations in KIT from selection of clones
  - ↑ renal clearance of imatinib → ↓ trough levels → ↓ tumor suppression
- Sunitinib blocks the TK receptor VEGF (vascular endothelia growth factor)
- 50 mg po od for 4 out of every 6 weeks.
- Response to sunitinib higher for C119 patients with
  - Primary KIT EXON 9
  - Wild-type KIT / PDGFRA mutation
  - KIT EXON 13 or 14 mutations
- AEs
  - General
    - Fatigue
    - Fever
  - Skin
    - Mucositis
    - Hand-foot syndrome (acral erythema)
  - GI
    - Abdominal pain
    - ↑ lipase, amylase
    - Nausea, vomiting
    - Tumor bleeding, perforation
  - Renal
    - Rena toxicity
  - Endocrine
    - Hypothyroidism (~30% at 1 year)
  - CVS
    - Hypertension (47%)
    - ↓ LV ejection (28%)
    - CHF (8%)

Sorafenib

- Use for resistance to imatinib, as well as resistance to sunitinib
- TK inhibitor acting on
  - KIT (part of the c-kit receptor, a membrane TK [tyrosine kinase]
  - PDGFR (platelet-derived growth factor receptor alpha)
  - VEGR (vascular endothelial growth factor)

➢ Prognosis

- Survival rates 5-year 87%
- Absolute benefit from imatinib is greatest in the high risk group
- The standard of care for GISTs is a curable surgical resection
- For patients who have a GIST tumor which is unresectable or borderline resectable
  - Retrospective studies have shown that imatinib given initially (Neoadjuvant TKI therapy) may shrink the tumor and the patient's lesion may now be operable, or may allow for a more conservative local resection
  - TKI Rx is considered to be first line therapy for metastatic GIST

Gems & Pearl

- URSO ↓ risk of gallstones by 40% after R-en-Y gastric bypass
- VBG (vertical banded gastroscopy) → pseudoachalasia

"When one door closes another opens.

Walk through to the next opportunity."

Grandad

OBESITY AND BARIATRIC SURGERY

Obesity

- Many different approaches are used to lose weight, and these vary widely in their success in helping the patient to achieve their ideal body weight.
- Basal energy expenditure approximately 0.8 kcal/min, or 1150 kcal / day
- Recommended daily energy intake, ~ 22 to 25 kcal / kg.
- Maintaining achieved purposeful weight loss is usually difficult.
- Optimal waist circumference
  - Women < 35 inches / 88 cm
  - Men < 40 inches / 102 cm
- BMI (wt (kg) / height (m^2))

Definition	BMI, kg / m^2
– Normal	< 25
– Overweight	25 – 29.9
– Obese	≥ 30
– Severe obesity	≥ 40 (or > 35 plus comorbidities)

- Give two processes rendering maintenance of weight loss so challenging.
  - Recidivism in proper calorie and food group intake
  - Reduction in basal energy expenditure as a result of weight loss, requiring an even further reduction in energy intake even though the ideal body weight has been achieved with the initial short term dieting.
- Give 4 evidence –based classes of pharmaceuticals used to treat increased BMI.
  - Centrally acting
    - Anti-depressants
    - Anti-epileptics
    - Serotonin 2 receptor agonist
    - Non-adrenergic sympathomimetics
    - Canaboid receptor antagonists

- ↓ food intake
- ↓ pancreatic lipase
- Control of hyperglycemia
- Dietary supplements

➢ Orlistat®

- Inhibits activity of pancreatic lipase
- 120 mg pot id, continued loss of weight at one year, as % of initial body weight
  - "placebo" (lifestyle changes) 5.5 to 6.6
  - Orlistat plus lifestyle changes 8.5 to 10.2
  - Therapeutic gain 1.9 to 4.7

- Give 5 AEs of Orlistat®.

Nuisance	– Cramps – Barborygmi – Flatus – Oil spotting on underclothes – Fecal incontinence
Nutrition	– ↓ absorption of fat soluble vitamins A, D, E
Liver	– Develop liver injury – 3 / 10^5 orlistat users
Kidney	– Oxalate-induced acute renal injury

- Give the mechanisms of the development of acute **oxalate-induced renal injury** in persons taking Orlistat®.

  - Orlistat → ↓ digestion of triglyceride (TG) → ↑ TG in stool → ↑ binding of Ca^{2+} - less Ca^{2+} -oxalate and ↑ luminal oxalate - ↑ absorption of oxalate → ↑ oxalate excretion by kidney, with ↑ deposition of oxalate in renal parenchyma

- Note: Ca^{2+} - oxalate in the lumen of the intestine require fatty acids removed from dietary TG (triglyceride) for the Ca^{2+} to become bound (Ca^{2+} - FA), the oxalate to be absorbed by the intestine, and excreted into the urine.
- The above description of the pathophysiology of oxalate damage to the kidney suffers from the problem that orlistat blocks pancreatic lipase, so fewer rather than more Fas are resent in the intestinal lumen to bind to the Ca^{2+} in Ca^{2+} - oxalate.

- Serotonin agonist, lorcaserin
  - Selective agonist of serotonin 2C receptor → ↓ food intake
  - 10 mg o bid provided
    - % of persons losing ≥ 5% of baseline weight in 1 year:
      - Lorcaserin (Lor) 48%
      - Pleacebo (PL) 20.3%
      - Therapeutic gain (TG) ~18%
    - % of persons maintaining weight loss in second year:
      - Lor 68%
      - PL 50%
      - TG ~18%

Target weight loss ~ 3 kg to 4 kg / year

    - ↓ SBP / DBP, HR, total / LDL cholesterol, CRP, fibrinogen, fasting glucose and insulin concentrations in blood
  - Because lorcaserin is a selective agonist of the serotonin 2C receptor, rather than the 2B serotonin receptor, there should be no lorcaserin-associated cardiac valvular disease (such as was seen with fenfluramine).

Abbreviations: CRP, C-reactive protein; DB, diastolic blood pressure; Lor, lorcaserin; PL, placebo; SBP, systolic blood pressure; TG, therapeutic gain

- Noradrenergic sympathomimetic drugs, phentermine and diethylroion
  - Only for short-term use (no more than 3 months)
  - ↑ satiety
    - ↓ food intake by acting on nerve terminals
    - ↑ release of norepinephrine
    - ↓ uptake of norepinephrine

- Anti-depressants
  - Bupropion
    - SR 300-400 mg / day
    - Especially useful for prevention of weight gain when smokers stop smoking
    - Alters the metabolism of norepinephrine
  - Fluoxetine
    - 60 mg po per day
    - SSRI (selective serotonin reuptake inhibitor)

- Antiepileptics: Insufficient evidence to recommend use at this time for weight loss

- Cannabinoid – 1 receptor antagonist
  - Clinically meaningful weight loss is off-set by psychiatric AEs
  - Not approved for use

- Diabetes – Treating drugs
  - Metformin very modest weight loss when used or prevention of diabetes (~2.5% of initial body weight)
  - Other oral diabetic drugs give only minimum weight loss

- Dietary supplements
  - Non-evidence-based use

Bariatric Surgery

- Indications
  - In a sentence, state the indications for bariatric surgery
    - BMI > 40 kg/m^2
    - BMI > 35 kg/m^2 plus comorbid complications

- Benefits

- Give the benefits of bariatric surgery.
  - ↓ all cause mortality rate (CV, CRC), as well as and other obesity-related cancers
  - ↓ diabetes
  - ↓ NAFLD histology score in > 80% (↓ fibrosis in 60%)
  - ↑ quality of life for patient

➢ Types of bariatric surgery

- Give the 3 major types of successful bariatric surgery.
  - Restriction procedures
    - VBG (vertical banded gastroplasty)
    - LAGB (laparoscopic adjustable gastric banding)
    - SE (sleeve gastrectomy)
  - Malabsorption-producing procedures
    - BPD (biliopancreatic diversion)
    - BPD / DS (BPD plus duodenal switch)
  - Mixed procedures
    - PYGB (Roux-en-Y gastric bypass)
    - Expected weight loss
      - RYGB
        - First 6 months 10 lbs to 15 lbs per month
        - 2 years
          - 65% of excess body weight, or
          - 35% of initial body weight
      - LAGB
        - 2 years
          - 45% of excess body weight, or
          - 25% of initial body weight

SO YOU WANT TO BE A GASTROENTEROLOGIST!

Patients with a partial gastrectomy and Roux-en-Y anastomosis may develop nausea, vomiting, bloating and early satienty. These symptoms are due to the stasis of food in the gastric remnant as well as the distal Roux jejunal efferent limb, especially, if the Roux limb is > 45 cm. This is called the “Roux-en-Y stasis syndrome”.

- Give the pathophysiology of the **Roux-en-Y stasis syndrome**.
  - The transection of the jejunum prevents the pacemaker wave generated in the duodenum from passing distal to the level of the transection → ↓ motility → ↓ stasis
  - Ectopic pacemakers in the Roux limb cause retrograde contractions

- Complications
  - The post-operative complications of bariatric surgery are often subdivided into 3 phases
    1) 1 to 6 weeks
    2) 7 to 12 weeks
    3) 13 to 52 weeks

- Name 3 bariatric procedures, and list 3 complications for each, and give 5 complications common to all bariatric surgical procedures.

- Specific procedures
  - Gastric bypass (Roux-en-Y)
    - Anastomotic leak with peritonitis
    - Stomal stenosis
    - Marginal ulcers (ischemia)
    - Staple line disruption
    - Internal and incisional hernias
    - Nutrient deficiencies (usually iron, calcium, folic acid, vitamin B12)
    - Dumping syndrome
  - Gastroplasty
    - GERD
    - Stomal stenosis
    - Staple line disruption
    - Band erosion
  - Gastric banding
    - Band slippage
    - Erosion
    - Esophageal dilation
    - Band infections
  - Biliopancreatic diversion
    - Anastomotic leak with peritonitis
    - Protein-energy malnutrition
    - Vitamin and mineral deficiencies
    - Dehydration

➢Complications common to all bariatric surgical procedures

- CNS
  - Psychiatric disturbance
- Lung
  - Atelectasis and pneumonia
  - Deep vein thrombosis
  - Pulmonary embolism
- CVS
- GI
  - Anemia
  - Diarrhea
  - Ulceration
  - GI bleeding
  - Stenosis
  - Gallstones
- Metabolic
  - Bone disease
  - Too rapid weight loss
- Surgical
  - Wound infection
  - Failure to lose weight
  - Mortality (0.5-1%)

Abbreviation: CNS, central nervous system

Adapted from: Klein S. *2006 AGA Institute Post Graduate Course*: pg. 175.

The gastroenterologist is often involved in the Phase 2 and Phase 3 medical problems.

- Give the Phase 2 and 3 post-operative **medical care** of the patient with bariatric surgery.

  - Nutrition
    - Eat slowly (< 1 oz per 10 minutes)
    - Eat solids, wait 30 min, then take beverage
    - Be aware o possible new food intolerance, e.g. red meat
    - Avoid snacks and high calorie fluid drinks, e.g. Coal “pop”
    - Identify and correct any vitamin D deficiency

- Beware alcohol use disorder (10% in second post-op year)
- Anticipate, possible deficiencies of
  - Thiamine
  - Copper
  - Zinc
  - Calcium (use calcium citrate po, which does not need gastric acidity for dissolution)

- Medications
  - Medicals need to be crushable, or liquid
  - If anti-diabetic therapy, use metformin po (only small changes in blood sugar)
  - Reassess need for treatment of GERD (GERD symptoms may improve with weight loss)
  - Reassess need for contraception
    - ↑ fertility as weight is lost
    - Menses may return
    - Consider use of non-oral hormonal
  - Reassess need for drugs for obesity-associated arthralgias
    - ↓ need or NSAIDs is possible
    - Use acetaminophen if arthralgias persist
    - Return of post psychiatric issues
- Be on lookout for
  - Psychiatric disorders
    - Emotional liability
    - Self-destructive behaviour
    - Bulimia
    - Somatization (nausea, vomiting)
  - GI disorders
    - Dyspepsia from development of stomal (aka marginal)
    - Nausea / vomiting
  - Cholelithiasis
    - 22% at 6 months post-op
    - Consider UCDA (ursodeoxycholic acid, ursodiol) 300 mg bid for 6 months

- Dumping syndrome
  - Avoid foods which are associated with causing symptoms (e.g. sugar, pop)
  - Eat slowly, “by the clock”
  - Take liquids at end of rather than during a meal
- Malabsorption
  - Iron
  - Vitamin B12
  - Calcium / vitamin D
  - Fat soluble vitamins
  - Lipids (including saturated and polysaturated fatty acids, and essential fatty acids)
- Prolonged vomiting
  - Only slowly advance intake to solid foods
  - Stomal stricture
  - Marginal ulcers
  - Small bowel obstruction, such as from internal hernia
  - Food intolerances
  - Somatization
  - Overrating
- New onset of heartburn, regurgitation, dysphagia
  - Gastric outlet obstruction from slippage of band, such as may occur if the patient had
  - An unrecognized or unrepaired hiatus hernia
- Hematemesis
  - Marginal ulcer
  - Mallory Weiss tear from vomiting
  - Severe esophagitis from partial gastric outlet obstruction
  - Band erosion through the wall of the stomach
- Slowing of initially satisfactory weight loss
  - Recidivism
  - Development of new and poor eating habits
  - Development of gastrogastric fistula

- Cosmetic and body image issues
  - Be smart: review the operative notes and any relevant post-operative imaging studies to be aware of the “lay of the land”.
  - Visualization may require the use of a narrower pediatric gastroscopy or colonoscopy.
  - ERCP of the biliopancreatic limb and retrograde evaluation of the by passed stomach is especially difficult after RYGB (Roux-en-Y gastric bypass).
  - This difficult is increasing with more use of “distal bypass”, with anastomosis of the biliopancreatic limb only 150 cm proximal to the ileocecal value.
  - Retrograde evaluation may be made easier with use of
    - Shapelock™ enteroscopy guide
    - Deep small bowel enteroscope
      - Double balloon
      - Spiral enteroscopy

Endoscopic Treatment

- Visualization may require the use of a narrower pediatric gastroscopy or colonoscopy.
- ERCP of the biliopancreatic limb and retrograde evaluation of the by passed stomach is especially difficult after RYGB (Roux-en-Y gastric bypass).
- This difficult is increasing with more use of “distal bypass”, with anastomosis of the biliopancreatic limb only 150 cm proximal to the ileocecal value.
- Retrograde evaluation may be made easier with use of
  - Shapelock™ enteroscopy guide
  - Deep small bowel enteroscope
    - Double balloon
    - Spiral enteroscopy

- Common Endoscopic Findings after Bariatric Surgery
  - RYGB
    - “gastritis” is common, but clinical significance is unclear
    - ~1/3 of symptomatic RYGB have a normal EGD
    - ~1/4 will have stenosis of stoma, usually 1 month after surgery
  - Be smart: review the operative notes and any relevant post-operative imaging studies to be aware of the “lay of the land”.

- Stoma
  - Narrowing
    - Symptomatic stomal stenosis
    - Bougie dilators or balloons, using guide wire TTS (through-the-scope placement)
    - Optimal operature diameter 10 mm to 15 mm
    - If multiple dilators needed, dilate slowly (up to 3 mm [3 French sizes] at each session, every 1 to 2 weeks until symptoms resolve
  - Reduction in size of enlarged stomas and pouches
    - Aim for stomal diameter ~ 12 mm
    - Objective is to reduce / eliminate symptoms e.g. slowing of expected weight loss from surgery; during syndrome)
    - Use sclerosants, suturing device

- Leaks
  - Fistulae, dehiscence of stale line, gastric leaks
    - Tissue apposition
      - Fibrin glue
      - Biomaterial (from pig intestine)
    - Stents
      - SEPS (self-expanding plastic stents)
      - SEMS (self-expanding esophageal metal stents)

- Band erosion
  - Nd:YAG laser
  - Scissors
  - Cutters (endoscopic)

- Marginal ulcer (MU) bleeding
  - Usually on jejunal side of gastrojejunal anastomosis
  - Early MU in 10%, late in 1%
  - Risk of MU associated with smoking, H. pylori infection, NSAIDs use
  - If bleeding occurs early after surgery, perform EGD in OR

SMALL BOWEL

CROHN DISEASE (CD)

(Please also see Colon chapter, Ulcerative Colitis)

- Demography
  - Incidence – $10/10^5$ per year in USA / Canada and Northern Europe
  - Prevalence – $200 / 10^5$
    – Female-to-male ratio of 1.3:1
- Terms

- Give the meaning of 7 of the following terms for adults with Crohn disease.

Term		Definition
○ Active disease		- CDAI >150
○ Remission		- Change in CDAI $\geq$ -100, CDA1$\leq$150
○ Relapse		- CDAI > 150 & ↑ CDAI by 70
○ Early relapse		- Relapse < 3 months after achieving remission on previous therapy
○ Pattern of relapse		- Infrequent $\leq$ 1 relapse/year
		- Frequent $\geq$ 2/year
○ GCS refractory disease*		- Active disease despite full dose GCS for 4 weeks
○ GCS dependent disease*		- Unable to reduce GCS below the equivalent of prednisone of 10 mg/day (budesonide 3 mg/d) with 3 months of starting GCS, without recurrent active disease - Relapse within 3 months of stopping GCS (early relapse)
○ Morphological recurrence†	0	No lesions
	1	<5 aphthous ulcers
	2	>5 aphthous ulcers with normal mucosa between the lesions, or skip areas of larger lesions, or lesions confined to the ileocolonic anastomotic lining (< 1 cm)
	3	Diffuse aphthous ileitis with diffusely inflamed mucosa
	4	Diffuse ileal inflammation with larger ulcers, nodules or narrowing

Term	Definition
○ Extent of disease	- Localized: < 30 cm in extent - Extensive: >100 cm in total extent
○ Colitis unclassified	- (do not use the term “indeterminate colitis” which is used for operative specimens) A change in diagnosis from Crohn colitis to UC during the first year; occurs in 10-15% of cases.
○ Risk factors for recurrence	- Smoking, prior appendectomy, family history of IBD, perhaps the use of OCA, NSAIDs, antibiotics, pregnancy, ± stress

* *assumes exclusion of disease-specific complications.*

† *hyperemia and edema alone are not signs of recurrence*

Abbreviations: CDAI, Crohn disease activity index; GCS: glucoscorticosteroids; NSAIDs, non-steroidal anti-inflammatory drug; OCA, oral contraceptive agent; UC, ulcerative colitis

- Clinical
  - Diarrhea 90%
  - Pain 90%
  - Bleeding 50%
  - Weight Loss 85%
  - Fever 60%
  - Malaise 40%

  - Perianal disease occurring before intestinal inflammation, 24%
  - Proximal intestinal Crohn disease and distal disease
    - Early 1/3, no
    - Late 3/3, yes
  - Intra-abdominal abscess in ~25% of Crohn patient during the lifetime of their disease
  - Angular cheilitis, 8%
  - PSC (primary sclerosing cholangitis) does occur in Crohn disease (4%), especially Crohn colitis

- Give the mechanism of the lung conditions associated with Crohn disease.
  - Crohn disease is associated with reactive airway disease ("asthma") and with COPD (chronic obstruction pulmonary disease, because of the "… commonality of bronchus-associated lymphoid tissue and gut-associated lymphoid tissue" (Feldman M., et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. Saunders/Elsevier, Philadelphia, 2010, page 1955).

Natural History of Crohn Disease in North America

- At any given point in time following the first year of the disease
  - Activity
    - High 10%
    - Low 25%
  - Remission
    - 65%

- Give the features used to make a distinction between ulcerative colitis (UC) and Crohn disease (CD).

Feature	UC	CD
Clinical Features		
- Malaise, fever	+	+++
- Abdominal pain	+	+++
- Diarrhea	+	+++
- Rectal bleeding	+++	+
- Weight loss	+	++
- Signs of malnutrition	+	++
- Perianal disease	+	++
- Abdominal mass	o	++
- Risk of colorectal cancer	+++	++
- Lymphoma	-	+
Intestinal Complications		
- Stricture	Rare (exclude CRC)	Common
- Fistulas	Very Rare	Common
- Sepsis	Uncommon	Common
- Toxic Megacolon	May occur	Uncommon
- Perforation	Uncommon	Uncommon
- Hemorrhage	Common	Uncommon
- Rate of malignancy	Increased	Increased

Feature	UC	CD
○ Radiological Features		
- Mucosal Ulceration	Superficial	Superficial
- Fissures	Never	Characteristic
- Strictures or fistulas	Rare	Common
- Ileal involvement	Never ("backwash ileitis")	Narrowed/common
- Distribution	Continuous, Symmetric	Discontinuous, Asymmetri
○ Endoscopic Features		
- Aphthous and linear ulcers	Rare	Common
- Cobblestone appearance	Never	Common
- Pseudopolyps	Common	May Occur
- Distribution	Continuous	Discontinuous
- Rectal Involvement	Characteristic	Occasionally occurs
○ Histopathology of ulcerative colitis (UC) and Crohn disease (CD)		
- Crypt	Distorted Abscesses	Normal or focally distorted abcesses
- Inflammation type	Acute and chronic	Normal or chronic
	Continuous between and within biopsies	Patchy between and within biopsies
- Depth	Superficial	Transmural
- Granuloma	No	Yes

- Give predictors of future severe Crohn disease.
  - Clinical
    - Perianal disease at the time of diagnosis
    - The need to use steroids, and
    - Age under 40 years
  - Genetic
    - Mutation in NOD_2/CARD 15 (ileal stricture, future need for surgical resection)
      - HLA-DRB1* 0103 allele
      - Increasing number of abnormal serological markers (such as pANCA, ASCA, AMCA, ALCA, anti-omp-c, anti-CB_{1R1}, anti-I_2)

➢ Pathology

- Give 7 macroscopic features seen on colonoscopy which suggest the diagnosis of Crohn disease.
  - Thickening of the intestinal wall
  - Fat wrapping of mesentery
  - Confluent deep linear ulcers, aphthoid ulcers
  - Deep fissures
  - Fistulas
  - Cobblestoning
  - Skip lesions (segmental disease)
  - Strictures
  - Rectum typically spared

➢ Serology

- Give the serological markers which predict a specific phenotype of Crohn disease.

Serological marker	Crohn phenotype
○ ASCA (anti-Saccharomyces cerevisiae antibody)	– Small intestine
○ Anti-cBiR1	– Stricturing and interally penetrating disease
○ Anti OmpC (anti – E. coli outer membrane porin C	– Perforation (fistula)
○ pANCA (perinuclear antineutrophil cytoplasmic antibodies)	– "UC-like" Crohn disease

➢ Diagnostic imaging

- Give the performance characteristics of CT enterography (CTE) for Crohn disease.
  - Performance characteristics of CTE for the diagnosis of Crohn disease
    - Sensitivity, 82%
    - Specificity, 89%

- Give the three criteria on CTE which correlate best with the endoscopic evidence of active Crohn disease.

  - CTE and the best criteria for diagnosis of active Crohn disease:
    - Mural enhancement
    - ↑ attenuation (↑ density of perenteric fat)
    - "comb" sign (segmental dilation of the vasa recta of a loop of intestine)

- Give 10 tools to **assess disease activity** of CD.

  - Symptoms
    - Quality of life
    - CDAI – a child of logistic (not so logical) regression
    - No correlation between CDAI and CDEIS (endoscopy score)
    - Lehman score – complications
  - Laboratory
    - Serum C-reactive protein (CRP)
      - ↑ CRP (> 20 mg/L), ↑ ESR (> 15), (8X ↑ risk of relapse if both markers positive: negative predictive value 97%)
      - ↑↑↑ CRP – suspect abscess
      - CRP may be used to guide therapy and follow-up
    - ↑ α_2 globulin, α glycoprotein, ↑ TNF
    - Urinary lactulose / mannitol (L/M) excretion test
    - Stool markers (calprotectin, lactoferrin, TNF – related to extent and degree of ulcerated intestinal surface, with high predictive value for colonic inflammation, and for upcoming clinical relapse
  - Endoscopy
    - Predicts change (but how do we operationalize this in practice)
    - Confocal
    - Biopsy
  - Diagnostic imaging (DI)
    - Cross-sectional imaging
    - CT enterography is being replaced by MR enterography (MRE) MARIA α CDEIS for small bowel disease
    - WBC flux through gut (useful in CD-colitis and UC; not useful in small bowel-CD)

- Ultrasound suggestive of active IBD
  - Wall thickening
  - Inflammatory fat
  - Lymphadenopathy
- Colour doppler US
  - Inflammation induces neoangiogenesis
  - Active vs inactive CD 200% ↑ vascularity
  - ↑ blood flow → ↑ inflammation
  - Fractional blood volume
- Peak intensity
- AUC (area under curve)
- Area under wash in (AUWI) and washout (AUWO)

Source: Lakatos PL, et al. Am J Gastroenterol 2012; 107: 579-588.

➢ Differential

Small Bowel	Colon
○ Backwash ileitis in ulcerative colitis	○ Acute self-limited colitis
○ Iatrogenic (drugs) - Ischemic (oral contraceptives, ergotamine, amphetamines, phenylephrine, cocaine) - NSAID-related ulcer or stricture	- Indeterminate colitis - Ulcerative colitis - Behçet disease - Microscopic colitis - Collagenous colitis - Lymphocytic colitis
○ Gynecological disorders - Ectopic pregnancy - Endometriosis - Ovarian cyst or tumour - Ovarian torsion - Pelvic inflammatory disease - Tubo-ovarian abscess	- Diversion colitis - Pouchitis - Diverticular disease associated segmental colitis - Graft-vs.-host disease (GVHD) - Solitary rectal ulcer syndrome (SRUS)
○ Ileitis associated with spondyloarthropathy	

Small Bowel	Colon
○ Infection - *Actinomycosis israelii* - *Anisakis simplex* - Cryptococcosis - Cytomegalovirus - *Histoplasma capsulatum* - *Mycobacterium avium* complex - *Mycobacterium tuberculosis* - Neutropenic enterocolitis - *Salmonella* - *Yersinia enterocolitica* - *Yersinia pseudotuberculosis*	○ Infection - Viral ▪ Cytomegalovirus (CMV) ▪ Herpes (HSV) - Bacterial ▪ Clostridium difficile ▪ Salmonella species ▪ Shigella species ▪ Yersinia enterocolitica ▪ Campylobacter jejuni ▪ Vibrio perahaemolyticus ▪ Aeromonas hydrophila ▪ Neisseria gonorrhoeae ▪ Listeria monocytogenes ▪ Chlamydia trachomatis ▪ Syphilis ▪ Staphylococcus aureus ▪ Escherichia coli (0157:H7) - Protozoan ▪ Amebiasis (ENT amoeba histolytica) ▪ Balantidiasis ▪ Schistosomiasis - Fungal ▪ Histoplasmosis ▪ Candidiasis
○ Infiltrative disorders - Amyloidosis - Eosinophilic gastroenteritis	
○ Other inflammatory disorders - Appendiceal abscess - Appendicitis - Cecal diverticulitis	
○ Neoplasms - Carcinoid tumour - Cecal or ileal adenocarcinoma - Lymphoma - Lymphosarcoma - Metastatic cancer	
○ Lymphoid nodular hyperplasia	○ Iatrogenic (drugs) - Enemas - Laxatives - OCA - Ergotamine - Amphetamines - Phenylephrine - Cocaine - Nonsteroidal anti-inflammatory drugs (NASIDs) - Penicillamine
➢ Torsion of the appendiceal epiploica	

Small Bowel	Colon
○ Vascular disorders - Behçet syndrome	- Gold - Methyldopa
○ Ischemia (radiation, drugs); acute enteritis, chronic enteritis, stricture; chronic mesenteric ischemia); focal segmental ischemia	○ Ischemia (radiation, drugs)
○ Henoch-Schönlein purpura ○ Vasculitis (polyarteritis nodosa, Churg-Strauss syndrome, systemic lupus erythematosus, Takayasu's arteritis, Wegener's granulomatosis, lymphomatoid granulomatosis, giant cell Arteritis, rheumatoid vasculitis, Thromboangiitis obliterans)	○ Infiltration - Amyloidosis - Eosinophilic colitis - Chronic granulomatous disease - Sarcoidosis - Neutropenic colitis ○ Neoplasms ○ Lymphoid nodular hyperplasia - Carcinoid tumour - Cecal or ileal adenocarcinoma - Lymphoma - Lymphosarcoma ○ Metastatic cancer

Abbreviation: CMV, cytomegalovirus; HSV, herpes simplex virus; NSAID, nonsteroidal inflammatory drug

Printed with permission: Sands, B. *Sleisenger & Fordtran's gastrointestinal and liver disease: Pathophysiology/ Diagnosis/Management* 2006*:* pg. 2475.; and Su, Chinyu and Lichtenstion, Gary R. *Sleisenger & Fordtran's gastrointestinal and liver disease: Pathophysiology/Diagnosis/*Management 2006: pg. 2514.

➢ Treatment

Because it is increasingly recognized that "attacks " or flares of IBD may be associated with enteric infection, anticipate the MCQ examining whether you appreciate this association and are prepared to act upon this association, rather than the reflex action of placing every IBD patient with recurrent symptoms on corticosteroids, immunosuppressants , or biological.

- Give 5 micro-organisms which may cause what appears to be a **recurrence** of IBD

o Toxin	- Clostridium difficile - Salmonella - Shigella - Campylobacter - Yesinia
o Special request	- Escherichia Coli O157: H7
o Ova and parasites	- Including Entamoeba histolytica, especially in - First Nations persons, or patients visiting from endemic areas including Southern USA
o Viruses	- CMV (cytomegalovirus)

- Give 6 causes of the diarrhea which relate to the patient's Crohn disease.
  - Active CD
  - Mesalamine-(5-ASA) associated diarrhea
  - SIBO (small intestinal bacterial overgrowth from associated dysmotility, fistula, stricture)
  - Bile salt malabsorption (choleretic diarrhea)
  - Steatorrhea
  - Temporary lactase deficiency
  - Infection
    - C. difficile
    - CMV
    - HSV
  - Medical
    - Drugs used to treat Crohn disease
    - CO_2 laser ablation
    - Hyperbaric O_2
    - Injection of silver microspheres with antibiotic

- Surgery
  - Seton placement
  - Glue
  - Fistulotomy
  - Endorectal advancement flap
  - Fecal diversion
  - Proctocolectomy

Abbreviations: DRE, digital rectal examination; EUA, examination under general anaesthesia; EUS, endoscopic ultrasound; PF, perianal fistulae

➢ **Mesalamine and Salazopyrine**

- The 5-ASA products have been largely replaced by other therapies to induce or to maintain remission in CD.

- Give the anatomical location of the release in the GI tract of 5 of the orally administered 5-ASA products.
  - Mesalsal®/Salofalk®: terminal ileum (pH > 6)
  - Asacol®: terminal ileum; cecum (pH > 7)
  - Pentasa®: release begins in jejunum
  - Dipentum® and sulfasalazine: colon (requires colonic bacteria to cleave the diazo bond in the drug)
  - Balsalazide® (available only in the US): colon
  - MMX – colonic release; note: not to be used in pregnancy
  - Generic 5-ASA (modeled after Asacol): terminal ileum, but may be released at pH 5.5 (in proximal GI tract which is the potential problem with it)
  - Sulfasalazine: colonic bacterial breakdown of diazo bond

Note: Meta-analyses of 5-ASA in active CD: statistically superior to placebo, but an 18 CDAI unit difference is not thought to be clinically meaningful. (Hanauer SB, Stromberg U. *Clin Gastroenterol Hepatol* 2004;2:379-88)

- Give the factors affecting adherence to 5-ASAs in patients with ulcerative colitis (while this has been studied for 5-ASAs, the general principles may apply to other medications)

➢ Risk factors that are difficult to modify

- Age
- Gender
- Patient agreeableness
- Education level
- Recent disease course
- Immunomodulator use (if required for remission)
- Previous adverse events attributed to medication

➢ Potentially modifiable risk factors

- Cost of co pay and other barriers to refilling medications
- Treatable depression
- Physician- patient relationship
- Dosing regimen

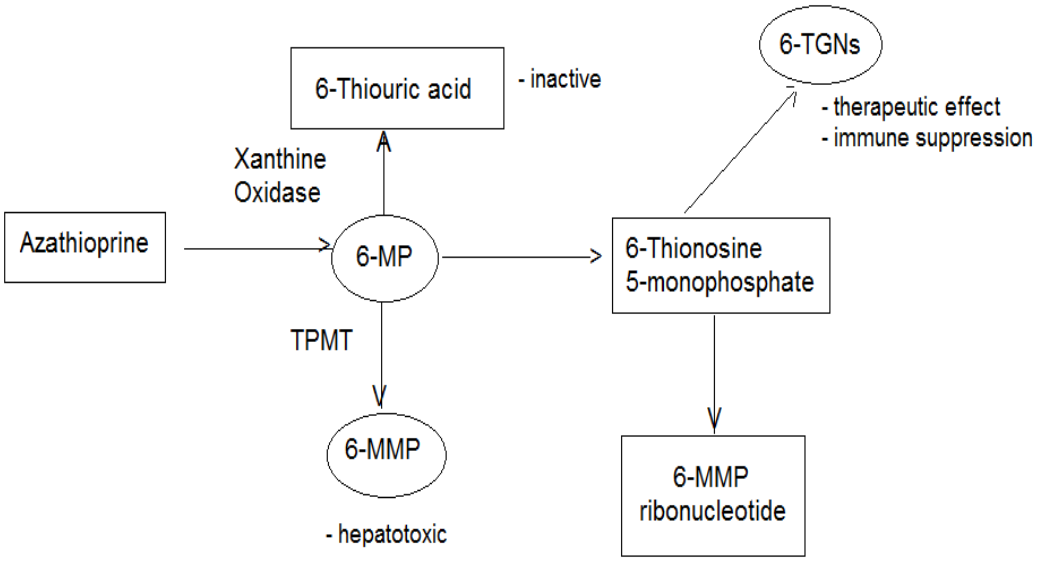
Printed with permission: Higgins PD, Rubin DT, Kaulback K, et al. Aliment Pharmacol Ther. Systematic Review: Adherence to 5- ASA, flares and costs in UC. *Journal Compilation* 2009;29:255.

➢ **Corticosteroid Therapy** for IBD (approximate percentages)

	30 Day	1 Year
Failure of steroid withdrawal (relapse at dose reduction or within 30 days after end of treatment)	25	-
Prolonged Response	~32	49
GCS Dependence	28	22
Surgery	38	29
Induction of clinical remission (4-16 wk)	75%	

- **Azathioprine (AZA) and 6-MP**

➢ Overview of thiopurine metabolism



- Azathioprine is non-enzymatically converted to 6-MP.
- Xanthine oxidase catalyzes hepatic first-pass oxidation of 6-MP to 6-thiouric acid (inactive).
- 6-MP then passes into systemic circulation
- 6-TGNs are active metabolites of 6-MP that do not undergo oxidation and are produced by HGPRT.
- TPMT inactivates 6-MP, and produces therapeutically inactive but hepatotoxic 6-MMP.
- TPMT competes with HGPRT for 6-MP substrate.
- The 6-TGNs have therapeutic and potentially toxic hematologic effects by integrating into IDNA (and interrupting replication), and by inhibiting de novo purine synthesis.
- In persons with reduced TDMT activity, the risk of myelotoxicity when using the standard rather than a reduced dose of AZA/6-MP is increased 4-fold
- In support of measuring AZA metabolites (such as 6-TG), weight-based dosing of AZA/6-MP still underestimates the dose 50% of the time (Morales A, Salguti S, Miao CL, et al. *Inflamm Bowel Dis* 2007;13:380-5

Printed with permission: Camilleri M. The role of pharmacogenetics in nonmalignant gastrointestinal diseases. Nat Rev Gastroenterol Hepatol. 2012;9(3):173-84. Figure 2.

- Give 3 potential risks and their likelihood of occurrence with the use of immunosuppression in CD.
  - 3% of allergic reaction including pancreatitis and hepatitis, usually within the first month intolerance to medication (ie headache, nausea, malaise) that requires drug withdrawal in 10%
  - 20-25 % risk of leucopenia
  - Drug interaction: allopurimol, 5-ASA
  - Increase levels of 6-TG; possible increased immunosuppression ad risk of malignancy when given with anti-TNF therapy
  - Increase in relative risk of small bowel lymphoma (controversial)
  - Lack of response

- Give different ways of **monitoring** during azathioprine therapy to reduce these risks.
  - Gene assay that measures the thiopurine methyl transferase (TPMT) genotype(mutation)
  - TPMT enzyme assay
  - 6-TGN (metabolic products) (6-thio guanine nucleotides, active metabolite)
  - Access CBC, liver enzymes
  - Dosage
    - AZA 2.5 mg/kg per day, continued indefinitely in patients who have achieved remission.
    - Dosage conversion of AZA to 6-MP ~50%
    - Allopurinol blocks xo; when ↓ XO; more 6-M is converted to 6-TG, so dose of 6-TG needs to be decreased.
    - Dose reduction or discontinuing AZA may be necessary if there develops bone marrow suppression (2%) or abnormal liver tests (0.5%).
    - Steroid-non-respondent, adding AZA ↑ likelihood of response ~50%
  - If patient is steroid-dependent, adding AZA decreases steroid requirement by ~70%.
  - Maintenance: AZA vs PL, RR of relapse – 0.4 to 0.6 absolute risk reduction of relapse -23%; NNT ~5
  - 3 months for therapeutic effect to be achieved

- AZA po = IV effectiveness

	WBC, x 10 (g)/L	Platelets, x 10(g)/L	ALT transaminases
– Stop reduction	<4	<120	
– Stop AZA	<3	<80	> 50% of ULN (upper limit of normal) ↑ bilirubin (cholestasis)

- Note: If jaundice develops AZA, the AZA should be stopped, and not restarted
- There is no direct therapeutic benefit for continuing 5-ASA to AZA when the AZA is used for 5-ASA failures.
- Some patients may be continued on 5-ASA while on AZA because 5-ASA → ↑ TG concentrations, and using the 5-ASA may allow the dose of AZA to be reduced and thereby possibly ↓ risk of adverse effects due to immunosuppression.

- Give the approximate percentage of patients reported from meta-analysis of trials of AZA / 6-MP to achieve and to maintain remission in CD.

	AZA / 6-MP	Placebo	TG	OR	NNT
Meta-analysis active*	54	33	21	2.36	5
Meta-analysis maintenance	67	52	15	2.16 4.13*	7

* 17 weeks necessary; **, optimal dose, 2.5 mg/kg

- Threshold level of 6-TG of 230 to 260 pmol / 8 x 10^8 RBC to achieve remission with TG of 26% (62% vs 36% placebo); aim for a ratio of 6-MMP: 6-TG of < 10
- Azathioprine/6-MP are <u>not</u> generally recommended for inducing remission in active CD or for preventing relapse in quiescent CD
  - Mixed data (2 trials, no benefit in preventing relapse (RR = 0.64; 95% CI = 0.34 – 1.23), yet 3 withdraw trials showing benefit (RR = 0.39; 95% CI = 0.21 – 0.74)

Abbreviations: OR, odds ratio; NNT, number needed to treat; TG, therapeutic gain

- Give the reasons to measure metabolites of AZA/6-MP to explain failure of AZA / 6-MP.
  - 70% - ↓ 6-TG: too low a dose
  - 25% - ↓ 6-TG + ↑ 6 MMP: predominant metabolism by TPMT
  - 5% - ↓ 6-TG + ↓6-MMP; poor adherence

6-TG	6-MMP	Interpretation
N	N	– Therapeutic dosing
		– TPMT high / low (90%)
		– Target 6-TG > 235
		– Myelosuppression when 6-TG > 450
↓	↓	– Non-compliant
		– Under dosing
↑	↑	– Over-dosing
		– Allopurinol or ACE inhibitor blockage of xanthine oxidase
↓	↑	– ↑ TPMT activity
		– High / high inheritance (1%)
		– Hepatotoxicity if 6-MMP > 5700
↑	↓	– ↓ TPMT activity
		– Low / low inheritance (95%)

Abbreviations: 6-TGN, 6-Thioguanine nucleotides; 6-MMP, 6-methyl Mercaptopurine; MP, Mercaptopurine

Adapted from: Spiegel BM. Acing the GI board exam. Slack Incorporated 2009, page 95-97.

- **Methotrexate (MTX)**
  - Hepatic fibrosis
    - With mean cumulative dose of MTX > 2.5 g, only minimal hepatic toxicity
    - Risk of hepatic fibrosis with MTX: ↑ by alcohol, obesity, diabetes
  - Reproduction
    - Women
      - Abortifacient, teratogenic
    - Men
      - Toxic to sperm
  - Lung
    - Rare cases of interstitial pneumonitis

- Give the approximate odd ratios of the risk of opportunistic infections in CD using standard pharmaceutical agents.

	Odds Ratio
o Any medication (5-ASA, AZA/6MP, Steroids, MTX, Infliximab)	3.50
o One medication	2.7
o Two medications	9.4
o 5-ASA	0.98
o Corticosteroids	3.4
o AZA/6MP	3.1
o MTX	4.0
o Infliximab	4.4

Adapted from: Toruner M, et al. Presented at DDW 2006; and van Asche et al. *Gastroenterology* 2007; 132:A-103.

- Give 15 gastrointestinal complications of immunosuppression with azathioprine or methotrexate (<u>not</u> including glucocorticosteroids).
  - Infection
    - CMV, HBV, HSV, EBV (PTLD)
    - Candida albicans, tropicalis
    - Yersinia enterocolitica
    - *C. difficile*
    - Microsposidia
  - Strongyloides stercoralis
    - H. pylori
    - TB
  - Mucosal injury
    - Diarrhea
    - Ulceration (AZA or MMF-induced slowing of intestinal cell turnover); may also result of concomitant intake of other medications, e.g. NSAIDs, steroids,
  - Colon: diverticular disease → diverticulitis
  - Perforations (upper or lower GI tract)

- Liver
  - Hepatitis
  - Methotrexate-associated fibrosis
- Biliary tract
  - Thickened gallbladder wall
  - Sludge
  - Stones
  - Dilated ducts
  - Hydrops
- Pancreatitis
  - Drugs (AZA, CyA)
  - Infection (CMV)
  - Pancreatitis
  - Hypercalcemia
  - Cholelithiasis)
- GI malignancy
  - Lymphomas (including Malt lymphoma, hepatosplenic lymphoma)
  - Kaposi sarcoma
  - Colorectal cancer
  - Post-transplant lymphoproliferative disorder (PTLD) (EBV)

Abbreviations: AZA, azathioprine; CyA, cyclosporin A; EBV, Ebstein Barr virus; PTLD, post-transplant lymphoproliferative disorder.

Adapted from: Helderman J, and Goral S. *J Am Soc Nephrol* 2002; 13: 277-87.

- Give 5 **immunosuppressive agents** commonly used in gastroenterology or hepatology (for example for Crohn disease, ulcerative colitis, autoimmune hepatitis), and for each give their mode of action, common toxic effects, and recommended monitoring.

Agent	Mode of action	Monitoring	Toxic effects
○ Prednisone	- Alter gene transcription ▪ Steroid response elements (SRE) ▪ Cytokine inhibitors (IL-1, IL-2, IL-6, TNF, and IFN gamma)	BP, BS, annual eye exam, DEXA scan	(see previous question)

Agent	Mode of action	Monitoring	Toxic effects
○ Azathioprine	- ↓T and B cell proliferation - ↓ purine synthesis (↓DNA/RNA)	White blood cell count, liver enzymes	Bone marrow suppression, hepatotoxicity
○ Cyclosporin (CyA), tacrolimus	- Calcineurin inhibitor: - ↓ IL-2-dependent T cell proliferation	Blood level of CyA, cholesterol, magnesium, Creatinine, BP, BS	Renal, neurologic, hyperlipidemic, hypertension, hirsutism
○ Sirolimus (Rapamycin)	- ↓ MTOR, which disrupts IL-2 induced intracellular signaling in lymphocytes	Blood level	Neutropenia, thrombocytopenia, hyperlipidemia
○ Methotrexate	- Folate antimetabolite (↓DNA)	Liver biopsy after 1,500 mg (only 2 years maintenance therapy)	Hepatic fibrosis Bone marrow suppression
○ Mycophe-nolate mofetil (Cellsept)	- ↓ T and B cell proliferation by ↓ with purine synthesis	White blood cell count	Diarrhea, bone marrow suppression
○ OKT3	- Blocking of T cell CD3 receptor - ↓ effector T cells and T regs - Prevent stimulation by antigen	$CD3^+$ count	Cytokine release syndrome, pulmonary edema, increased risk of infections
○ IL-2 receptor blocker	- Competitive inhibition of IL-2 receptor on activated lymphocytes		Hypersensitivity reactions with basiliximab

Abbreviations: BP, blood pressure; BS, blood sugar; DEXA, DEXA scan for bone mineral density; IFN, interferon; IL, interleukin; LEs, liver enzymes; MTOR, mammalian target of rapamyacin; TNF, tumour necrosis factor.

Adapted from: Martin P, and Rosen HR. *Sleisenger & Fordtran's gastrointestinal and liver disease: Pathophysiology/Diagnosis/Management* 2006: pg. 2049.

Biologics in Crohn Disease (CD)

- Overview of anti-tumor necrosis factor antibodies (anti-TNF; aka TNF-β, tumor necrosis factor blocker)
  - Adalimumab (ADA): Recombinant human IgG1 monoclonal antibody against TNF Certolizumab (Cer)
  - Certolizumab pegol (Cert): Humanized monoclonal antibody Fab fragment against TNF lacks a Fc region
  - Infliximab (IFX)
    - Chimeric IgG1 monoclonal antibody against TNF
    - 75% human, 25% murine sequences
    - Destroys activated effector cells by apoptosis
  - Given by IV infusion
    - Biological T1/2 ~ 10 days
    - Median time response ~ 2 weeks
    - Median duration of response ~ 12 weeks
  - Indication
    - Induction of moderate-to-severe CD
    - Maintenance of remission
    - Treatment of CD fistula
      - Co-therapy with antibiotics useful for severe perianal disease, including perianal fistula, rectovaginal fistulas
    - Otherwise unresolving joint (arthritis, arthralgia), eye (iritis, uveitis) and skin (pyoderma gangrenosum) complications, as well as continued idiopathic fever
  - Approximate outcome in initial responders (80% of ITT)

Induction	Response	2/3
	Remission	1/3
	Mucosal healing	1/3
Maintenance (1 to 2 years)	Remission	1/3
	Dose escalation of INF	1/3
	Steroid free	1/2
	- with concomitant immune suppression	2/3
	- without IMS	1/3

- **Anti – TNF** antibody therapies (infliximab, adalimumab, and certolizumab) are effective in inducing remission in ambulatory patients with moderately-to-severely-active CD (RR = 0.87; 95% CI = 0.80 – 0.94)
  - At preventing relapse in quiescent luminal CD
  - Cessation of fistula drainage
  - Infliximab is effective in prevention of relapse in healed fistulizing CD (RR of relapse = 0.71; 95% CI = 0.65 – 0.76).
  - "There were no statistically significant differences in indirect comparisons between infliximab, adalimumab and certolizumab"
  - "Biological therapy is indicated in steroid-refractory, steroid-dependent and for immunomodulator-refractory inflammatory bowel disease and in patients intolerant to these therapies" (3)
  - "Drainage of a perianal or an intra-abdominal abscess is essential.
- **Natalizumab** (anti-α4 integrin antibody) is effective at inducing remission in ambulatory patients with moderately-to-severely active CD (RR of no remission = 0.88; 95% CI = 0.83 – 0.94), and in prevention of relapse in quiescent CD.

Adapted from: Bebb JR and Scott BB, Aliment Pharmacol Ther 2004; 20: 151-159; Talley NJ et al., Am J Gastro 2011; 106: S2-S25; Lichtenstein GR et al., Am J Gastroenterol 2009; Ford AC et al., Am J Gastro 2011; 106: 590-599; Khan KJ et al., Am J Gastro 2011; 106: 630-642; Ford AC et al., Am J Gastro 2011; 106: 644-659; D'Haens GR et al., Am J Gastro 2011; 106: 199-212; Ford AC et al., Am J Gastro 2011; 106: 601-616.

- Suggestion
  - Most management criteria for use of TNFB (TNF blockers, i.e. anti-TNF biologics) require failure of immunosuppressants
  - Suggestion
    - Continue thiopurine for 6 months after starting TNFB, then taper and stop thiopurine, while continuing TNFB longterm; or
    - Continue thiopurine plus TNFB combination for CD patinets with poor prognosis
      - Males
      - Young age of diagnosis of CD
      - Ileal disease
      - Early need for glucocorticosteroids
      - Fistulising CD
      - Smokers

- Deep ulcerations
- Site
  - Esophagus
  - Stomach
  - Extensive disease
- Clinical / laboratory
  - Malnutrition
  - ↓ serum albumin
  - ↑ CRP

TNF-α Inhibitor Studies (a selection of the earlier important studies)

- Give the code name of 10 studies of biological treatments for CD, and indicate the objective of each study.

TNF blocker	Objective for use	Name of study
➢ Infliximab	○ Induction	– ACCENT I
	○ Maintenance	– ACCENT II
	– Fistulising disease	
	○ Switching IFX → ADA	– SWITCH
		– GAIN
	○ EIM – multiple studies	
	○ Concomitant immunosuppression	– SONIC
	○ Post-operative prophylaxis	
➢ Adalimumab	○ Induction	– CLASSIC-I
		– CHARM
	○ Maintenance	– CLASSIC-I
		– EXTEND (induction, remission, mucosal healing)
		– ADHERE
		– Multiple predictors for loss of response
	○ EIM	– CARE
	○ Concomitant immunosuppression	– ND
	○ Fistular closure	– ACCESS
		– CARE
	○ Switching	– ND

TNF blocker	Objective for use	Name of study
➢ Certolizumab	○ Induction ○ Maintenance	– PRECISE 1 – PRECISE 2 – PRECISE 3 – PRECISE 4
	○ Fistula closure	– PRECISE 2
	○ SWITCH INF → CER	– WELCOME

Abbreviations: EIM, extraintestinal manifestations; ND, no data

➢ Dosing

○ Infliximab	– 5 mg/kg IV per treatment at wk 0, 2 and 6, then q 8 wk dosing interval may be shortened for loss of clinical response or dose increased from 5 mg/kg per day to 10 mg/kg per day
○ Adalimumab	– 160 mg SC at wk 0, 80 mg wk 2, then 40 mg q 2 wk (160/80/40 mg) dosing interval may be shortened for loss of clinical response
○ Certolizumab Pegol	– 400 mg SC wk 0, 2, 4 then q 4 wk

In the absence of direct head-to-head comparative studies of infliximab (IFX), Adalimumab (ADA) and Certolizumab (ERT), what are the pivotal **points in selection** of a TNFB (TNF blocker) in CD?

➢ IFX
- ○ Greatest experiment data
- ○ Full range of benefit: induction, maintenance, fistulising disease, safety

- ADA
  - Sparse data on
    - Concomitant use of immunosuppression
    - Post-operative recurrence
    - Benefit of switch ADA → IFX
- CET
  - Disappointing data for evidence of benefit for induction
  - Sparse data on
    - Concomitant use of immunosuppression
    - Post-operative recurrence

- Give 10 factors associated with **loss of response**, or need for **dose escalation** of adalimumab
  - Patient
    - Male
    - ↑ BMI
    - Long duration of disease
    - Smoker
    - Family history of CD
    - EIM
    - Long duration of disease
  - CD
    - Isolated colonic disease
    - Higher CDAI
    - No “deep” remission at 12 wk
  - Drugs
    - Concomitant use of steroids
    - Previous use of TNFB
    - Previous non-response to infliximab
    - Low serum trough level of adalimumab

Abbreviations: BMI, body mass index; CD, Crohn disease; CDAI, Crohn disease activity index; EIM, extraintestinal manifestation; TNFB, tumor necrosis factor blocker (anti-TNF)

- Give 6 risk factors associated with **time-to-relapse** in patients with Crohn disease who are in clinical remission on maintenance therapy with both infliximab and anti-metabolites, and then who stop infliximab
  - Patient
    - No previous surgical resection
    - Male sex

- Laboratory
  - Hemoglobin level ≤ 145 g/L
  - Leukocyte count > 6 x 10^9 per L
  - CDEIS > 0
  - hsCRP level ≥ 5 mg/L
  - fecal calprotection level ≥ 300 µg/g`
- Drugs
  - infliximab trough level ≥ 2 mg/L
  - Corticosteroids use 6-12 months before infliximab discontinuation
- Clinical relapse rate (%) as a function of the number of risk factors
  - < 4 risk factors: < 20%
  - 4 risk factors: ~ 40%
  - 5-6 risk factors: ~ 80%
- > 6 risk factors: 100%

Printed with permission: de Chambrun GP, et al. IBD in 2011: Advances in IBD management--towards a tailored approach. Nat Rev Gastroenterol Hepatol. 2012;9(2):70-2. Box-1.

- Start high or start low

The controversy of the "**Step-up" vs. "Start High**" approach to the use of anti-TNF biological in CD needs to take into consideration.

- Only about ½ of CD patients ever have serious-enough disease activity to require the use of corticosteroids.
- Just because the patient does not have symptoms does not mean she / he does not have active inflammation.
- It is the active inflammation which usually leads to the complications of the strictures and fistulae.
- Perianal disease may rise from inflammation in the rectal crypts, with no evidence of mucosal disease.
- Only sensitive diagnostic imaging techniques can determine if there is no ↑ blood flow to an area of the bowel, an indirect marker active inflammation.
- It is likely that acquiring mucosal healing in CD will alter its natural history.

- The concept now for the treatment of CD is to provide "personalized targeted therapy" which reflects the patient's chance of having high risk disease.
- For CD patients with high risk disease, start anti-TNF therapy early.

➢ Step Away from Step-Up Therapy in Crohn Disease: Suggestions
- Much less use of 5-ASA, glucocorticosteroids
- Much more use of immunosuppressants, biologics

- Give two common anti-TNF-α **skin rashes**.
  - Psoriatic lesions; ± pus
  - Eczematous lesions

- Give 7 **live vaccines** which should **not** be given while the IBD patient is on anti-TNF therapy.
  - Bacilli Calmette-Guerin (BCG)
  - Herpes Zoster Virus (HZV)
  - Nasal influenza (inhaled)
  - Japanese encephalitis
  - Measles, mumps, rubella (MMR)
  - Polio (oral)
  - Rotavirus
  - Typhoid (oral)
  - Vaccinia (smallpox)
  - Varicella
  - Yellow fever
  - Anti-TNF therapy vs **placebo** (PL)

	Duration of treatment, weeks	Clinical response		Mucosal healing
		Anti-TNF	PL	
Response	8	64% and 66%	29%	55%
Remission	30	39% and 32%	15%	57%
Response	54 (durability)	45% and 44%	20%	22%
Remission	54	34%	17%	

- Give the **relative contraindications** to anti-TNF therapy.
  - Pre-existing severe immunosuppression
  - Allergy to anti-TNF
  - Intestinal stenosis
  - Fistulizing disease with abscess
  - Fistulae to bladder
  - Untreated active infection (TB, HBV, HCV)
  - Multiple sclerosis (MS), optic neuritis
  - Congestive cardiac failure (New York grade III, IV)
  - Lymphoma
  - Acute liver failure
  - Cancer in the past

Abbreviations: HBV, hepatitis B viral infection; HCV, hepatitis C viral infection; MS, multiple sclerosis; TB, tuberculosis.

➢ Definition

- Give a definition for **primary and secondary infliximab failures** (IFX) in patients with inflammatory bowel disease (IBD); outline their proposed mechanisms.
  - Primary – No response to induction therapy, possibly due to high pre-treatment TNF-α levels, inadequate dose of IFX (low trough IFX concentration), or TNF-α independent inflammatory pathways
  - Secondary (Loss of symptomatic response after initial successful induction therapy)
  - Mechanisms
    - Antibody to IFX (especially with on-demand IFX infusions)
    - Increased clearance (rapid metabolism) of IFX
    - Inadequate dose of IFX (low trough IFX concentration) non-TNFα dependent inflammatory pathways
    - Development of IBD-related complications e.g. stricture, abscess
    - Non-IBD related symptoms e.g IBS, SIBO, bile acid wastage, c. difficile infection

Useful background: Response and secondary failure after anti TNF-α therapy

➢ Approximately 1/3 of primary responders lose response over course of 6-12 months
  - Change in behavior of disease
  - Development of antibodies to therapy
  - Loss of response to anti-TNF mechanism of action

- There have been no reports of hepatosplenic T-cell lymphoma in IBD patients on monotherapy with anti-TNF therapy, or on a combination of infliximab or adalimumab with methotrexate
- If anti-TNF therapy is added to AZA or MTX because of failure to respond to these immunosuppressants, then it would appear to be reasonable to stop immunosuppressant once the anti-TNF therapy has been started, especially since withdrawal of aziothioprine and continuation of the infliximab (IFX) alone has no effect on the continued response to IFX, as compared to patients on both IFX and AZA (Van Assche G, et al. *Gastroenterology* 2008:1861-8.) This issue remains controversial.
- For patients with secondary loss of response to IFX, switching to ADA gives "recapture" remission rates of 21% at 4 weeks and 40% at one year (Panaccione R, et al., DDW 2008, #920); switching from IFX to certolizumab pegol at 6 weeks gives a "recapture" response of 60% and remission of 40% (Reinisch W, et al. DDW 2008: #494)

Abbreviations: IBD, inflammatory bowel disease; IFX, infliximab

Combination of Biologic Plus Immunosuppressant

- Give the advantages and disadvantages of adding concomitant immunomodulators to anti-TNF therapy in Crohn disease (CD).

Advantages	Disadvantages
○ Benefit in steroid-dependent CD (SONIC) ○ Advantages of concomitant immunosuppressive therapy – ↓ antibody formation ▪ ATI (antibodies to infliximab), 28% ▪ ATA (antibodies to adalimumab), 3% – ↓ infusion of reactions – ↑ efficacy of biologic – ↑ duration of response	- ↓ duration of response (with episodic therapy) – No difference in short- or longterm responses to induction + maintenance therapy in refractory CD (ACCENT, CHARM, PREcISE) – No benefit with steroid-induction (COMMIT) – Risk of HSTCL with combination therapy ▪ Males > female 94% vs 6% ▪ Age: 90% < 3 yr, 10% > 35 yr – ↑ longterm toxicity ▪ Serious infections ▪ ↑ Risk of infections - Cost ▪ Malignancy

Patient groups	Risk of HSTCL
○ IBD patients on the thiopurines	1:45,000
○ Men < 35 yr exposed to thiopurines	1:1500
○ Men < 35 yr exposed to thiopurines plus anti-TNF	1:35,000

Abbreviation: Hepatosplenic T cell lymphoma

- Give the recommended dosing for adalimumab or certolizumab pegol, in patients with Crohn disease.

➢ Adalimumab

- 160 mg subcutaneously (SC) on day 1 of week 0, followed by 80 mg SC on day 1 of week 2.
- Patients who respond to this two week induction regimen should continue on a maintenance regimen of 40 mg SC every other week.
- Patients who have suboptimal response to 40 mg SC every other week may increase frequency of dosing to 40 mg SC weekly, or increase their dose to 80 mg every other week.
  - Subsequent response in 4-week nonresponders has not been established.
- Episodic dosing has not been evaluated, and may increase Immunogenicity
- For patients with secondary loss of response to IFX, switching to ADA gives “recapture” remission rates of 21% at 4 weeks and 40% at one year (Panaccione R, et al., DDW 2008, #920); switching from IFX to certolizumab pegol at 6 weeks gives a “recapture” response of 60% and remission of 40% (Reinisch W, et al. DDW 2008: #494)

➢ Certolizumab pegol

- Recommended dosing is 400 mg SC at weeks 0, 2, and 4 and then end 4.
  - No evidence of benefit for additional treatment at week 6 for nonresponders

- Patients who respond to the induction regimen should continue on maintenance dosing with 400 mg SC every 4 weeks.
  - Additional dosing schedules have not been evaluated in IBD but anticipate similar recommendations to other anti-TNFs regarding higher dose/reduced interval treatment. In patients with rheumatoid arthritis, changing the maintenance dosing schedule to 200 mg SC every 2 weeks increases drug exposure by approximately 50%

- Serious side effects of anti-TNF agents in Crohn disease

Event	Estimated frequency per 10^5
NHL (baseline)	20
- Also on IM	40
- Also on anti TNF in perspective	60
Death from sepsis	400
Tuberculosis	50

*Data on file, Centocor, Inc. TNF= Tumour necrosis factor; NHL= no Hodgkins lymphoma; IM= immunomodulator (azathioprine/6-mercaptopurine); HSTCL= hepatosplenic T cell lymphoma

Adapted from: Siegal, Corey A. *2009 ACG Annual Postgraduate Course* 2009:267-9.

- Surgery is commonly needed in persons with Crohn disease' 18% in the first year after diagnosis, and 80% after 20 years. The operative mortality is $80/10^5$, compared with a $40/10^5$ mortality rate for dying of sepsis from anti-TNF therapy (Siegel CA, et al. *Clin Gastroenterol Hepatol* 2006:1017-24.)
- Elemental, hydrolyzed and polymeric formulas are equally effective in the treatment of IBD (Zachos M, et al *Cochrane Database Syst Rev* 2007:CD000542.) (Or, 0, 33)

- Miscellaneous
  - ↑ colon cancer (CRC)
    - ↑ CRC risk with Crohn colitis or ileocolitis
    - Standardized incidence ratio of 26.6
    - ↑ risk of CRC in Crohn of colon similar to UC of same extent
  - ↑ mortality rate (per 10^5 person-years)
    - General population 497
    - Crohn disease 669

A patient may have an increased risk of infection if they are being treated with immunosuppressants or anti-TNF therapy.

- Give 4 conditions associated with an **increased risk of infection** in the patient who is not receiving immunosuppressants or biologicals (anti-TNF therapy).
  - Granulocytes (chronic granulomastous disease)
    - ↑ risk of invasion skin infections
  - Cell-mediated defects (e.g. HIV infection, ↓ CD4 T cells)
    - Viral or fungal infections
  - Immunoglobulins
    - Encapsulated bacteria
  - CFTR (cystic fibrosis)
    - Infection of sinuses and lung
  - Complement deficiency
    - Neisseria meningitides gonorrhea

Adapted from: Board Basics 3, 2012, page 9.

- Pediatrics
  - Infliximab and adalimumab are effective in pediatric CD in inducing and maintaining remission.
  - In pediatric UC, infliximab is effective in inducing and maintaining remission; adalimumab is effective for pediatric UC patients who lose response or are intolerant to infliximab.

Abbreviations: ADA, Adalimumab; IFX, Infliximab

- Give 4 common causes of **infertility in men** with inflammatory bowel disease.
  - Medications; sulfasalazine, 5-ASAs, methotrexate
  - Active inflammatory bowel disease
  - Poor nutritional status
  - Tobacco use
  - Alcohol use
  - Postsurgical complications

Printed with permission: Feagins LA, and Kane SV. *Am J Gastroenterol* 2009;104(3):773.

- Debunking some therapies
  - Best maintenance management of CD
    - Stop smoking!
  - No evidence for
    - Fish oil supplements
      - There is no benefit of fish oil in Crohn disease (Turner D, et al. *Cochrane Database Syst Rev* 2009;CD006320.; Feagan BG, et al. *JAMA* 2008:1690-7.)
    - SCFA (short-chain fatty acid) enemas (only useful in diversion colitis)
    - Transdermal nicotine particles to maintain remission (for UC patients who smoke and have mildly active UC, using nicotine patches may be beneficial while the patient stops smoking – on no sue in UC patients who are non-smokers)
    - Heparin
    - Enteral nutrition
      - Steroids are more effective than enteral nutrition in the treatment of active Crohn disease (Zachos M, et al. *Cochrane Database Syst Rev* 2007:CD000542.)
  - Still "on radar screen": more data needed
    - Methotrexate
    - Budesonide MMX
    - Trichuris suis (helminthes, from pigs)
    - Oral phosphatidylcholine
    - Anti-integrin antibodies
    - Thiazolidinediones (rosiglitazone)
    - Antibodies against IL-12, IL-23
    - MAd CAM (mucosal addressin cell adhesion molecule-1)
    - Numerous biologicals being tested in RCTs

SO YOU WANT TO BE AN IBDologist!

The thiazolidinediones (such as rosiglitazone) are used in patients with diabetes to control their hyperglycemia. There is not an increased risk of diabetes in UC, and the hyperglycemia noted in some UC patients on glucocorticosteroids is reversible.

- Give the mechanism thought to explain why rosiglitazone (a thiazolidinedione [thio]) has been shown in preliminary studies to be useful in mild-moderate active UC.
  - Thio → ↑ PPAR (peroxisome proliferator-activated receptors [or ligands]) → ↓ proinflammatory cytokines.

Mucosal Healing

- The clinical trials of agents used to treat IBD have used a variety of clinical scores heavily based on symptoms, measures of quality of life of the IBD-sufferer, appearance of the mucosa on diagnostic imaging, endoscopic imaging, or histopathology.
- With the observation that about two-thirds of patients with CD treated with TNF-β achieved mucosal healing (MH) on the colonoscopic visualization of the colon or terminal ileum, the question was raised whether MH by itself, independent of patient's symptoms or QoL, was an important outcome variable.

MH would be an important outcome if it were to be shown that MH was associated with reduced risk of recurrence (i.e. greater likelihood of maintenance of remission), reduced risk of extraintestinal complications), reduced risk of medical treatment-associated complications, longterm risk of hospitalization, surgery, or development of colorectal cancer (CRC).

In clinical trials, there has been no uniform standard for defining MH, no agreed-upon optimal time for assessing MH. As seen in Table below, the ranges are wide.

	CD		UC	
Drugs	Time * (wks)	MH (%)	Time * (wks)	MH (%)
5-ASA	-	-	4-8	25-71
Prednisone	4-9	0-27	-	-
AZA	16-96	40-73	26	53-69
MTx	12-60	36-38	-	-
IFX	4-104	29-100	8-52	62-71
ADA	12	27	8	30
CER	10	5-55	-	-

* time for endoscopic assessment

Abbreviation: ADA, adalimumab; CER, certolizumab pegol; IFX, infliximab; MH, mucosal healing; MTX, methotrexate;

MH is associated with more later steroid-free remission, but it is not clear if this correlates with fewer adverse effects, or better outcomes such as QoL, hospitalizations or surgery.

Associations of mucosal healing in CD	Improvement	
○ Fewer		
- No previous surgery	No	Modigtiani et al., 1990
- Previous surgery	No	Ruffolo et al., 2010
○ Less inflammation at 5 years requiring steroid use	No	Frøslie et., 2007
○ Less use of steroids		Baert et al., 2010
- Steroid-free remission and no flare at year 3 and 4	Yes (TG, 44%)	
- Steroid-free remission, no flare and no TNF-β at year 3 and 4	Yes (TG, 44%)	
- No new or persistently active fistulae	No	

How do these associatings with MH in CD compare with UC? About 90% of patients remain asymptomatic after achieving MH on once-a-day 5-ASA (Mezavant®), and after MH, 40% of UC patients remain asymptomatic (TG, 22%) (Lichtenstein & Rutgeerts, 2010; Kamm et al., 2008)

Abbreviations: TG, therapeutic gain (response in active treatment group minus response in placebo group; differences statistically significant)

- Give 6 treatments for **duodenal Crohn disease**.
  - PPIs
  - H_2-blockers
  - Sucralfate
  - Oral small bowel released 5-ASA (Pentasa®; not well supported by data)
  - Oral intake of 5-ASA enema
  - Systemic corticosteroids
  - Immune suppression
  - Anti-TNF
  - Endoscopic dilation of associated stricture
  - Surgery

- Treat associated nutrient deficiency, fluid and electrolyte imbalance
- Some CD patients with Anti-TNF therapy induced remission can be maintained with an immunomodulator, whereas others require schedule re-treatment with anti-TNF.
- If the patient loses response to one anti-TNF, they may respond to a different anti-TNF but with a lower response rate.
- If the patient becomes intolerant to one anti-TNF, they may be able to tolerate and respond to another anti-TNF.
- Lifetime additional risk of fatal cancer per diagnostic investigation
  - Abdominal radiograph 1/30,000
  - Barium follow-through 1/6,700
  - Barium enema 1/3,000
  - CT abdomen/pelvis 1/2,000

www. hpa.org.uk, quoted in table 5, Mowat C et al., Gut 2011; 60(5):571-607.

Clinical Scenario

A 25 year old female has had ileal Crohn disease for 3 years and has been taking no medications for the past 2 years. She smokes 1 pack of cigarettes per day. She presents to your office with 1 month of abdominal pain and diarrhea. You get a small bowel follow through and it reveals a short segment of ileal disease. You prescribe entocort 9 mg/day. You see her again in 1 month and she feels completely well and you begin tapering her entocort. Give 5 options for further therapy at this time.

- Taper entocort to 6 mg/day, then to 3 mg then stop before 12 months
- Taper entocort completely off and leave her on no medications
- Taper entocort off and use Pentasa® 4 gm/day
- Start azathioprine or 6-mercaptopurine as maintenance agents
- Start methotrexate as a maintenance agent (advise contraception)
- Start anti-TNF, with or without immune suppression (controversial)
- Stop smoking (equivalent to immunosuppression)
- Discuss contraception, pregnancy planning
- Antibiotics, probiotics
- Surgery
- Symptom control
- Education, including Crohn and Colitis Foundation (CCFC)

Did You Know?!

- 5-ASAs (mesalamines)
  - May rarely ↑ diarrhea symptoms in IBD
  - Are not steroid-sparing
  - Combining po plus pr 5-ASA therapy is better than just oral therapy for mild-moderate UC
  - Don't stop 5-ASAs suddenly: may cause a relapse
  - 5-ASA is not recommended for inducing remission in active CD, or for preventing relapse in quiescent CD

- Steroids (corticosteroids)
  - Budesonide, as Entecort is useful for Crohn disease (CD) of ileum and right colon.
  - Do not use in acute UC, because left colon does not benefit.
  - MMX budesonide may be useful for acute UC.
  - No steroid of any kind should be used long-term (. 3 month) for UC or CD.
  - Effective at inducing remission in active CD (RR = .46*)
  - Standard corticosteroids are more effective than budesonide at inducing remission in mild-to-moderately-active CD (RR = 0.82, 95% CI = 0.68 – 0.98)
  - Budesonide is not recommended to prevent relapse in quiescent CD, but steroid-related adverse effects are more common (RR = 1.64; 95% CI = 1.34 -2.00).

* "Both trials of standard glucocorticosteroids in CD remission reported a statistically significant effect, but because of heterogeneity between studies, the overall effect was not significant (RR = 0.46; 95% CI = 0.17 – 1.28)

Did You Know?!

- Cyclosporin (aka cyclosporine)
  - Cyclosporin is effective for severe UC, but not for Crohn colitis.
  - Cyclosporin s as effective as infliximab for evere UC, but with ↓ AEs (fewer adverse effects)
  - Cyclosporin is **not** recommended for use in patients with CD (neither active nor quiescent disease).
- Immuno-suppressants
  - Allopurinol and ACE inhibitors increase the blood level of 6-MP and methotrexate, and may ↑ neutropenia.
  - **Methotrexate IM** (intramuscular) is effective at inducing remission in active CD, and at preventing relapse in quiescent CD.
  - Antibiotics
    - **Antibiotics** have shown a statistically significant effect at inducing remission (RR of active CD not being in remission = 0.85, 95% CI = 0.73 – 0.99), and at preventing relapse in quiescent UC (RR of relapse = 0.62; 95% CI = 0.46 – 0.84), but various antibodies have been studied and no one class can be recommended.
    - "When starting biological therapy in patients with CD naïve to thiopurines the combination of IFX [infliximab] and AZA [azathioprine] is better for induction of remission and mucosal healing over 1 year…the optimal maintenance strategy after this induction regimen and whether the same applies to other agents remains unknown."
  - CMV
    - May cause an acute exacerbation of UC / CD
    - Colonic mucosal biopsies may show the CMV taken from normal appearing mucosa.

Did You Know?!

- C. difficile
  - May cause an acute exacerbation of UC / CD.
  - C. difficile may occur in UC / CD patients who have not recently been on antibiotics or salazopyrine
  - The abnormal mucosa arising from the infection may occur just on the right side of the colon.
- Immunosuppression
  - The incidence of abnormal PAP smears is increased in women with IBD (Kane S, et al. *Am J Gastroenterol* 2008:631-6), possibly related in part to the use of immunosuppression and biologics
- NSAIDs
  - May worsen symptoms of UC or CD, and may cause a relapse of disease, and may cause colitis in their own right.
- Anti-TNFs
  - Meta-analysis has shown that the rate of non-Hodgkins lymphoma (NHL) is $61/10^5$ patient years in persons on anti-TNF therapy plus immunomodulators, a rate similar to that from the use of immunomodulators (Siegel CA, et al. Clin Gastroenterol Hepatol 2009; 7(2):168-74)
  - There have been no reports of hepatosplenic T-cell lymphoma in IBD patients on monotherapy with anti-TNF therapy, or a combination of infliximab or adalimumab with methotrexate

SO YOU WANT TO BE A GASTROENTEROLOGIST!

It used to be taught that TNFB should not be given to CD patients with strictures, stenosis, or symptoms / signs of obstruction (SSOs). And yet, increasingly it is being suggested that biologics being use in this setting.

- Give the rationale for the paradigm shift that TNFB may be used in CD patients with SSOs.
  - Multivariant analysis of the TREAT registry data revealed that the predictors of SSOs in CD were
    - ↑ severity
    - ↑ duration
    - Ileal disease
    - Recent use of steroids
    - Note: the use of maintenance TNFB (IFX) was not a predictor for the occurrence of SSOs

Smoking

- Give 3 examples of the benefit (%) of non-smoking in the patient with Crohn disease.

	Smoking	
Groups	No	Yes
○ Response within first 2 months	73	22
○ Concurrent immunosuppressants	74	39
○ Response lasting longer than 2 months	59	6
○ Concomitant immunosuppressants	65	18

- Give the influence of smoking (S) and immunosuppressants (IM) on the outcomes of CD patients with fistula

	Responses	
Variable	Rates	Duration
○ Smoking (S)	Non S = S	Non S > S
○ Immunosuppression (IM)	IM = non IM	IM = non IM

IBD – Fertility, Pregnancy and Lactation

- Fertility conception / pregnancy
  - Colectomy and ileoanal anastamosis increases infertility 3-fold (Waljee A, al. *Gut* 2006:1575-80.)
- Investigation
  - Flexible sigmoidoscopy during pregnancy does not increase the risk of premature labour (Cappell M, Colon V, Sidhim O. *Dig Dis Sci* 1996;41:2353-61.)
- Dietary
  - Although the only contraindications to vaginal delivery in Crohn disease is active perianal disease, the likelihood of having a Caesarean section is increased 1.5 times above that of non-IBD women (Cornish J, et al. *Gut* 2007:830-7).
  - Having an extensive episiotomy at delivery may contribute to the 18% risk of a woman developing perianal disease after childbirth (Iinyckyj A, et al. *Am J Gastroenterol* 1999:3274-8).
- Outcomes
  - In a community based study from northern California, the activity of IBD at conception usually carries through the pregnancy as well as post-partum period.
  - While earlier studies have suggested poor outcome of pregnancy in IBD patients with active disease (Miller J. *J R Soc Med* 1986:221-5.), this has not been confirmed more recently (Mahadevan U, et al. *Gastroenterology* 2007:1106-12)
- Breast feeding
  - Only 29-44% of IBD patients breast feed their infant (compared to an American standard of 60%), and 43% of those mothers who breast feed their babies flared, possibly because 74% of those who flared had stopped maintenenace medications (Kane S, Lemieus N. *Am J Gastroenterol* 2005:102-5).
  - Breast feeding may or may not be a risk factor for the development of Crohn disease in the infant (Klement E, et al. *Am J Clin Nutr* 2000:1342-52.; Jantchou P, Turck D. *Am J Clin Nutr* 2005:485-6)
- IBD in child
  - The transmission of IBD from parent to child is low
    - One parent with IBD; transmission risk is 7%
    - Both parents have IBD, 37% risk of transmission (Yang H, et al. *Gut* 1993:517-24.)

Abbreviations: IBD, inflammatory bowel disease; IFX, infliximab

- Classify the medications used in patients with IBD. For 5 of these, give the FDA category for pregnancy, and recommendations for breast feeding.

Drug	FDA category	Recommendations for breast feeding
Adalimumab	B	LHD
Amoxicillin/clavulanate	B	Probably compatible
AZA/6-MP	D	LHD
Balsalazide	B	Yes
Ciprofloxacin	C	LHD
Corticosteroids	C	Yes
Cyclosporin	C	**No**
Diphenoxylate	C	**No**
Infliximab	B	LHD
Loperamide	B	Yes
Mesalamine	B	Yes
Methotrexate	**No**	**No**
Metronidazole	B	**No**
Olsalazine	C	LHD
Rifaximin	C	LHD
Sulfasalazine	B	Yes
Tacrolimus	C	LHD
Thalidomide	**No**	**No**

During **pregnancy, No** thalidomide, or methotrexate

During **breastfeeding,**

No cyclosporin, methotrexate, metronidazole, thalidomide, or dephenoxylate

Abbreviation: LHD, limited human data

Printed with permission: Kane SV. *2008 ACG Annual Postgraduate course book*: pg. 27.

Pregnancy and Lactation in Crohn disease

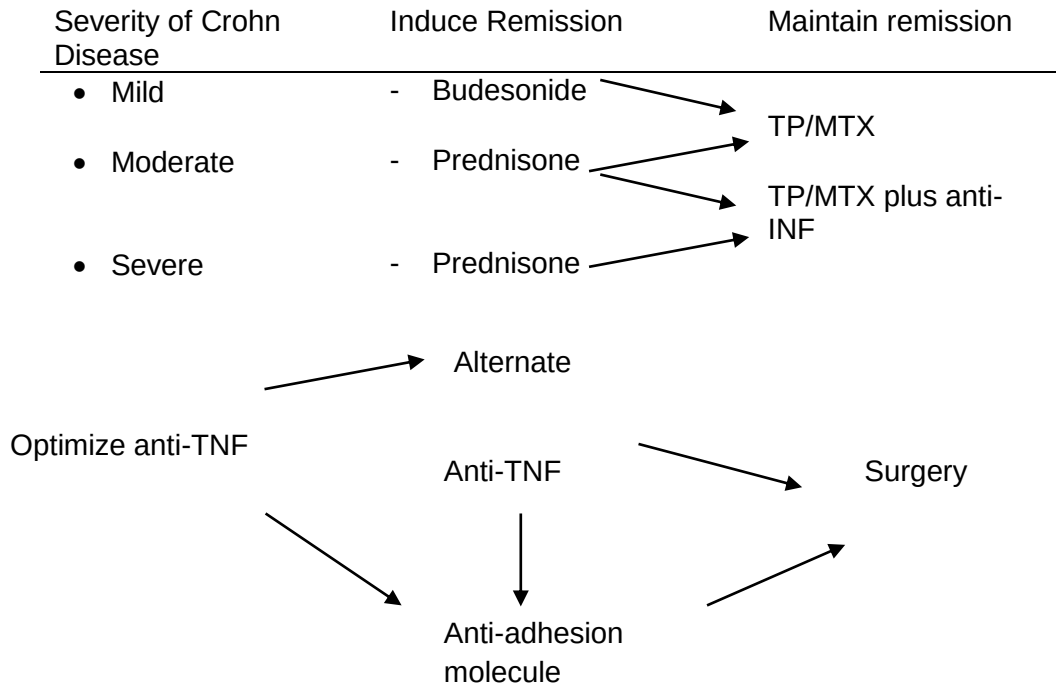
Anti-TNF	Use during conception in men and women	Use during pregnancy by mother	Use during breast feeding by mother
• Infliximab	OK	OK	OK
• Adalimumab	OK	OK	NASD
• Certoizumab pegol	OK in women NASD in men	OK	OK

Abbreviation: NASD, not adequate safety data

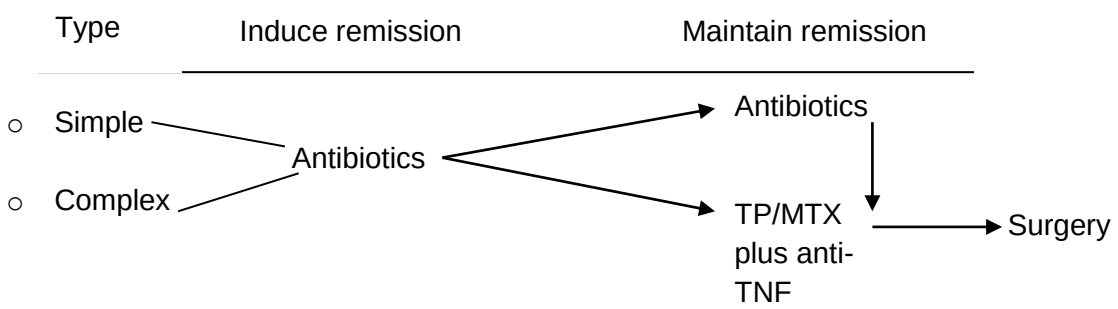
Adapted from Mahaderan U et al., Am J Gastroenterol 2011; 106: 214-223.

- Treatment

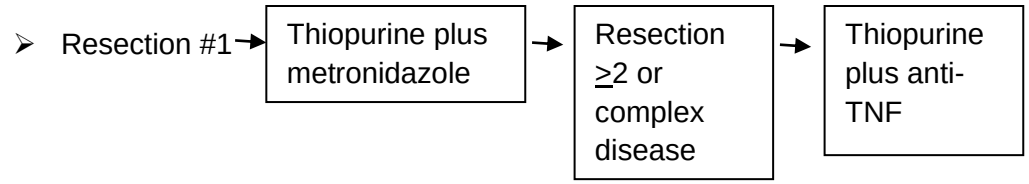
Algorithms In Crohn Disease



Perianal Crohn Disease Fistulas



Post-Operative Resection for Ileal/ Ileocecal Crohn Disease



Note: there is growing evidence to proceed directly to TP + anti-TNF

Abbreviations: MTX, methotrexate; TNF, tumour necrosis factor; TP, thiopurine (including 6-mercaptopurine)

Adapted from: Chande N. Personal Communication.; and Bernstein CN. *AMJ Gastroenterol* 2015;110:114-126.

- Useful Trivia re: Pregnancy and Lactation
  - Colectomy and ileoanal anastamosis increases infertility 3-fold (Waljee A, al. *Gut* 2006:1575-80.)
  - The incidence of abnormal PAP smears is increased in women with IBD (Kane S, et al. *Am J Gastroenterol* 2008:631-6).
  - The transmission of IBD from parent to child is low
    - One parent with IBD; transmission risk is 7%
    - Both parents have IBD, 37% risk of transmission (Yang H, et al. *Gut* 1993:517-24.)
  - While earlier studies have suggested poor outcome of pregnancy in IBD patients with active disease (Miller J. *J R Soc Med* 1986:221-5.), this has not been confirmed more recently (Mahadevan U, et al. *Gastroenterology* 2007:1106-12)
  - The activity of IBD at conception usually carries through the pregnancy as well as post-partum period (Young 09).
  - Although the only contraindications to vaginal delivery in Crohn disease is active perianal disease, the likelihood of having a Caesarean section is increased 1.5 times above that of non-IBD women (Cornish J, et al. *Gut* 2007:830-7).
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SMALL BOWEL OBSTRUCTION AND ILEUS

Post-operative Ileus

- Give 6 factors/approaches that have been shown to ↑ recovery from postoperative ileus.
  - Surgery
    - Thoracic epidural local anesthetics
    - Intravenous or wound local anesthetics
    - Goal-directed fluid therapy and avoiding fluid excess
    - Laparoscopic surgery
    - Avoid NG tubes
  - Patient
    - Laxatives
    - Peripheral opiod antagonists
    - Early oral feeding
    - Chewing gum
    - Minimize opiod use

Adapted from: Kehlet, H. *Nat Clin Pract Gastroenterol Hepatol* 2008 ;5: pg 552-558.

- In the patient with Crohn disease (CD) who presents with sub-acute, small bowel obstruction (SBO), give the structural causes, diagnostic procedures, and the managements.

➢ Causes
  - Active CD
  - Stricture
  - Bands and adhesions
  - Fruit pits
  - Gallstone ileus
  - Enterolith
  - Hernias

➢ Diagnostic procedures
  - Plain abdominal films
  - Conventional CT
  - CT enterography
  - MRI enterography
  - Small bowel (gastrograffin) x-ray
  - Abdominal ultrasound
  - Doppler ultrasound
  - FDG-PGT (18F- flurodeoxyglucose positron emission tomography [PET])
  - Capsule endoscopy (penalty, because of suspected stricture)

Abbreviations: PET, positron emission tomography

- In any patient, and not necessarily one with Crohn disease, give causes of small or large intestinal ileus.
  - Infection
    - Intra-abdominal or systemic sepsis
  - Inflammation
    - Appendicitis, diverticulitis, perforated duodenum
    - Lower lobe pneumonia
  - Ischemia
    - Mesenteric arterial embolus or thrombosis, mesenteric venous thrombosis, chronic mesenteric ischemia
  - Metabolic
    - Hypokalemia, hyponatremia, hypo/ hypermagnesemia, hypo/ hypercalcemia

- Trauma
  - Laparotomy, laparoscopy, lower rib fractures
  - Lumbar compression fracture
- Drugs
  - Anticholinergic agents, clozapine, diltiazem, narcotics, phenothiazines
- Electrolyte Abnormalities

Adapted from*:* Turnage Richard H., et al. *Sleisenger & Fordtran's gastrointestinal and liver disease: Pathophysiology/Diagnosis/Management* 2006: pg. 2671.

- Management
  - Treatment of inflammatory CD (avoid anti-TNF)
  - Through-the-scope balloon dilation
  - Adjuvant steroid injection into inflammatory narrowing
  - Expandable metal stents
  - Stricturoplasty
  - Open or laparoscopic surgical resection

Fistulae

- Give different schemes for the **classification of gastrointestinal fistulae**, based on anatomical location, output volume, and etiology.

Scheme	Classification
Anatomical location	– Internal, external – Low, high – Simple, complex
Output volume	– Pancreatic – Low (<200 ml/day) – High (≥200 ml/day) – Intestinal – Low (<500 ml/day) – High (≥500 ml/day)
Etiological	– Underlying disease

Printed with permission: Messmann H, et al. *Best Pract Res Clin Gastroenterol* 2004, pg. 811.

- Diagnostic tests
  - Digital rectal examination (DRE)
  - EUA (examination under general anaesthesia)
  - Pelvic ultrasound
  - Pelvic CT
  - Pelvic MRI
  - Sigmoidoscopy/colonoscopy
  - EUS
  - Barium studies (fistulogram, sinogram)
  - Cystoscopy

- Give the patient-related and fistula-related characteristics associated with spontaneous closure of gastrointesinal fistulae.
  - Patient characteristics
    - Low output (mL/day) <500
    - Young (<40 years)
    - Well nourished
    - Cause of fistulae
    - Anastamosis characteristics – anastamotic breakdown
  - Fistula characteristics
    - Lateral fistula
    - No incomplete disruption
    - No abscess near leakage
    - No distal obstruction
    - Fistula tract >2 cm
    - Non-epithelialised fistula tract
    - Enteral defect <1 cm
    - Fistula site: Oropharyngeal, esophageal, duodenal stump, pancreatobiliary, jejunal
    - Late post-operative leakage
    - Adjacent bowel healthy
    - No severe systemic diseases

Printed with permission: Messmann H., et al. *Best Pract Res Clin Gastroenterol* 2004, pg. 811.; and Hoffman KM, Furukawa M, Jensen RT. *Best Pract Res Clin Gastroenterol* 2005; 19: pg 677.

- Treatments
  - Medical
    - Drugs used to treat Crohn disease
    - CO_2 laser ablation
    - Hyperbaric O_2
    - Injection of silver microspheres with antibiotic
  - Surgery
    - Seton placement
    - Glue
    - Fistulotomy
    - Endorectal advancement flap
    - Fecal diversion
    - Proctocolectomy

Abbreviations: DRE, digital rectal examination; EUA, examination under general anaesthesia; EUS, endoscopic ultrasound; PF, perianal fistulae

MALNUTRITION

- Give approximate frequency of **nutritional deficiencies** in IBD (Crohn disease and ulcerative colitis)

  - The prevalence of malnutrition is ↑ in IBD: 6.1% in Crohn disease, 7.2% in ulcerative colitis, vs 1.8% in non-IBD controls (275-5). the adjusted odds ratio (OR) for malnutrition in IBD was 5.57 (95% CI 5.29-5.86), with a ↑ risk of malnutrition in those with fistulizing CD (1.65; 95% CI: 1.50-1.82), and in IBD patients who had undergone bowel surgery (1.37; 95% CI: 1.27-1.48).

  - Importantly, malnutrition is also associated with a ↑ length of hospital stay, increased hospital mortality (3.49: 95% CI: 2.89-4.23), and double the hospital costs.

- High risk (~ 70%)
  - Weight loss

- Medium risk (~ 40%)
  - Anemia
  - Folic acid
  - Hypoalbuminemia

- Iron
- Vitamin B12
- Vitamin D
- Zinc

➢ Low risk (~ 25%)
- Calcium
- Magnesium
- Vitamin A
- Vitamin E
- Vitamin K
- Selenium

Adapted from: Seidner, Douglas L. *2009 ACG Annual Postgraduate Course*: 271-276.

Mechanisms

- Give the mechanisms for **malnutrition** in persons with IBD.

  - Reduced oral intake
    - Disease-induced (e.g., postprandial abdominal pain and diarrhea, sitophobia, anorexia (↑TNF), nausea and vomiting)
    - Iatrogenic (e.g., restrictive diets, "fad" diets)

  - Malabsorption
    - Reduced absorptive surface (e.g., prior resection, diseased segments)
    - Small bowel bacterial overgrowth (SIBO; e.g., associated with strictures and bypassed loops, fistulae stasis)
    - Bile salt deficiency after ileal resection (e.g., impaired micelle formation and steatorrhea)
    - Lactase deficiency (e.g., associated with small bowel disease)
    - Drug-induced malabsorption
      - Cholestyramine (e.g., bile acids; fat; fat-soluble vitamins, including vitamin D and K)
      - Sulfasalazine (e.g., folic deficiency associated with reduced absorption and increased requirement related to hemolysis)
      - Steroids (e.g.. calcium absorption, and patient mobilization)
      - Methotrexate (e.g. nausea/vomiting)

- Increased nutrient losses
  - Protein-losing enteropathy
  - Diarrhea fistula losses of electrolytes, minerals and trace elements zinc, iron, calcium, magnesium, selenium
  - Gastrointestinal blood loss (e.g., iron loss)

- Increased requirements
  - Chronic inflammatory disease
  - Fever, abscess
  - Superimposed infection
  - Surgery

Printed with permission: Griffiths AM. *Best Pract Res Clin Gastroenterol* 2004;18(3): pg.519.

INFECTIOUS DIARRHEA

- Giardiasis + no plasma cell infiltration in submucosal on mucosa biopsy
  - Suspect CVID (common variable immunodeficiency)
- Lymphoma plus Campylobacter jejuni infection
  - Suspect IPSID (immunoproliferative small intestinal disease)

- Give infectious causes of terminal ileitis.
  - Tuberculosis
  - MAC
  - Yersinia
  - Campylobacter
  - Cryptosporidium

Cryptosporidiosis occurs in both immunocompetent and immunocompromised patients, and causes watery diarrhea. Because the Cryptosporidium infection usually involves the terminal ileum, there may be vitamin B12 deficiency.

- Give the CD4 counts at which cryptosporidiosis is likely to occur, at what level the infection should be treated, and with what.
    - CD4
        - < 180, cryptosporidiosis occurs in 10% of HIV-infected persons with diarrhea
        - < 50,treat with nitazoxanide

- Give the clinical presentation, causes, site of involvement, and fecal leukocytes of persons with inflammatory versus non-inflammatory infections.

Characteristic	Inflammatory diarrhea	Non-inflammatory diarrhea
Clinical presentation	-Bloody, mucoid small-volume diarrhea, tenesmus lower left quadrant abdominal cramps -May be febrile and toxic	Large-volume, watery diarrhea; no blood, pus or tenesmus. May have nausea, vomiting, cramps but no fever
Causes	*Shigella* spp., *Salmonella* spp., amebic colitis, *campylobacter* spp., EAEC, EHEC, EIEC, *Yersinia* spp., *Clostridium difficile*	Norovirus, rotavirus, *Vibrio cholerae*, *Giardia lamblia*, ETEC, enterotoxin-producing bacteria, *Staphylococcus aureus, Cryptosporidium parvum, Clostridium perfringens*
Site of involvement	Colon	Small intestine
Fecal leukocytes	Positive	Negative

Abbreviations: EAEC, Enteroaggregative *Escherichia coli*; EHEC, Enterohemorrhagic *Escherichia coli*; EIEC, Enteroinvasive *Escherichia coli*; ETEC, Enterotoxigenic *Escherichia coli*

Printed with permission: Navaneethan U. and Giannella R. *Nat Rev gastroenterol Hepatol* 2008(5): 637-647, Table 1.

Extraintestinal Manifestations of Enteric Infections

Clinical Challenges

A patient with Strongyloides stercoralis is treated with thiabendazole 25 mg/kg po bid for 3 days. The helminthic infection clears, but symptoms persist.

- Give the name of the likely co-infection causing persistence of symptoms.
  - HTLV-1 (human T-lymphotropic virus -1)

The patient with a short history of possibly infectious diarrhea will have a confirmed diagnosis from stool cultures or from the determination of 16S ribosomal DNA (rDNA) sequence. As sharp clinicians, it is always fun to speculate on the type of infection which will be found:

- Give the extraintestinal manifestations which may suggest the etiological of an acute enteric infection.

○ Yersinia	– Thyroid – Heart – Kidney	▪ thyroiditis ▪ pericarditis ▪ glomerulonephritis
○ Shigella, EHEC (enterohemorrhagic E. Coli, usually O157:H7	– Kidney / blood	▪ hemolytic-uremic syndrome
○ Arthritis (reactive)	– Salmonella – Shigella – Campylobacter – Yersinia	

Adapted from Feldman M., et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. Saunders/Elsevier, Philadelphia, 2010, Table 107.3, page 1848. Also please see Feldman M., et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. Saunders/Elsevier, Philadelphia, 2010, Table 107.8, page 1859 "Complications and Manifestations of Bacterial Enterocolitis".

Clinical Clues ("Buzz" words) for the cause of acute diarrhea

- Raw shellfish
  - Vibrio vulinficus, or V. parahemolyticus
  - Norwalk virus
  - May cause sepsis / death in patient with cirrhosis
- Chocolate milk
  - Hysteria monocytogenes
  - Severe disease
    - Elderly
    - Pregnant (abortion)
    - Immunocompromised
- Reheated fried rice
  - Bacillus cereus
  - Biphasic nausea / vomiting then diarrhea
- Undercooked hamburger
  - EAEC (Enterohemorrhagic E.Coli (EHEC) O157:H1
  - Associated with hemorrhagic colitis
    - HUS (hemolytic uremia syndrome)
    - HUS plus TTP (thrombotic thrombocytopenic purpura) may be precipitated by use of antibiotics
- Pet turtle / reptile
  - Salmonella infection
- Cruise ship
  - Norwalk virus (may be associated with shellfish)
- Camping
  - Giardiasis, particularity if drinking water from lakes used by beavers

Source**:** Spiegel BM. Acing the GI board exam. Slack Incorporated 2009, page 92-94.

Please see: Maclean C. Chapter 55. In: Therapeutic Choices. Grey J, Ed. 6th Edition, Canadian Pharmacists Association: Ottawa, ON, 2011, Table 2: Nausea in adults, page 731-733.

Please see: Fedorak RN, Gupta M, Borowiec AM. Chapter 57. In: Therapeutic Choices. Grey J, Ed. 6th Edition, Canadian Pharmacists Association: Ottawa, ON, 2011, Table 2: Diarrhea, page 759-761.

- Stool culture
  - Indications
    - When ↑ BM is a major inconvenience
    - > 4 BM / day
    - Fever
    - Blood, pus or mucus in stools
    - When symptoms persist for > 2 days
    - When the above indications apply, and results of culture will direct Rx
    - After stool cultures available – redirect Rx at specific organism(s)

  - Helpful Hints
    - Any cause of chronic diarrhea may lead to malnutrition, which is associated with atrophy of the thymic gland, and thus impaired T-cell-mediated immune response. This will weaken their natural body defense.
    - In the person with low CD4 counts, organisms that would normally cause only acute diarrhea may become chronic, and may become associated with extraintestinal symptoms
    - Clostridium difficile infection is common in the immune suppressed patients; not all labs' include C. difficile culture and toxin measurements in routine requests for stool culture – become familiar with what your laboratory does routinely.
    - Similarly, you may need to request stool examination for
      - Acid-fast smear
        - MAC (mycobacterium avium intracellular)
        - Cryptosporidium
        - Isospora belli
        - Cyclospora
      - Trichrome staining of stool for Microsporidium
    - Just as with TD (travellers' diarrhea), so also with diarrhea in the immune-compromised person, no etiology may be found in ~50%
    - In the situation of the HIV-infected person, this idiopathic group is sometimes referred to as "HIV-enteropathy" (the frequency of this diagnosis is reflected in part by just how thorough is the diagnostic investigation).

- Give the common **infectious causes** of chronic diarrhea which may be **diagnosed on mucosal biopsy.**

  - Small bowel
    - G.lamblia
    - Cryptosporidium
    - Microsporidium
    - MAC
  - Colon
    - C.difficile
    - CMV
    - HSV
    - Amebiasis
    - Schitosomiasis

SO YOU WANT TO BE A GI PATHOLOGIST!

A biopsy of the mucosa of the small or large bowel taken from a person with diarrhea is positive on PAS and acid-fast staining.

- Give the cause of acid-fast staining of the mucosa.

  - The cause of acid-fast staining would include
    - TB
    - MAC
    - Cyclospora

- Give the causes of PAS staining of mucosa, and suggest how these may be differentiated.

  - The causes of PAS-positive stain would include
    - MAC infection
    - Alpha-1 anti-trypsin deficiency
    - Whipple disease

  - Note: Whipple disease is PAS-positive, diastase-resistant

Stool Tests in Diarrhea

- Fecal (WBC and calprotectin)

- Give the performance characteristics of fecal leukocytes and calprotectin to predict the presence of an inflammatory cause of diarrhea

Characteristics	WBC	Calprotectin
o Sensitivity	70%	93%
o Specificity	50%	96%

Another Clinical Curiosity

- Give the "reach" of sigmoidoscopy / biopsy to detect the cause of chronic non-bloody diarrhea?
  - Sigmoidoscopy establishes the cause of chronic non-bloody diarrhea in only 15% to 20% (unless biopsy of mucosa is performed)
  - About 10% of patients with collagenous colitis have biopsy changes only in the proximal colon

  - What's the message
    - in the patients with diarrhea, perform full colonoscopy with biopsy to ↑ yield of
      - L-sided disease
      - Infection
      - Microscopic colitis

Clinical TIP

- Appendicitis-like symptoms, suspect Yersinia Enterocolitica
- Immunosuppressed patient, or outbreaks of diarrhea in immunocompetent persons, suspect Cryptosporidia

The stem of the MCQ describes the patient with sudden onset of diarrhea. You will likely be told how long after the onset that the patient is seen. You will likely be asked what treatment to use. Watch out – this is where they can put a noose around your neck…….unless you read this.

Ingestion	Time (hr) of onset of symptoms after ingestion	Likely organism
----------→	6	Staphylococcus aureus
		Bacillus cereus
----------→	8 to 12	Clostridium perfringes (canned food)
----------→	14	Virus, e.g. rotavirus, Norwalk, ETEC, EHEC (O157:H7)

Caution – The Treatment Noose

- EHEC
  - No antibiotics → HUS, TTP
  - No antidiarrheals (loperamide, diphenoxylate)
- C. difficile
  - No antidiarrheals → toxic megacolon

Abbreviations: TTP, thrombocytopenic thrombotic purpura; HUS, hemolytic uremic syndrome; EHEC (O157: H7), Enterohemorrhagic Escheichia coli); ETEC, enterotoxigenic E. Coli

During Pregnancy and Breast Feeding

Whats's safe

- Loperamide (Imodium ®)

What to avoid	Why
○ Diphenoxylate with atropine (**Lomotil ®**)	– Teratogenic in animal studies – Excreted in milk
○ **Bismuth subsalicylate**	– Salicylates absorbed in excess – May lead to multiple problems, including ▪ ↑risk of prenatal / neonatal mortality ▪ Neonatal hemorrhage ▪ ↓ birth weight of child

TRAVELLER DIARRHEA (TD)

- Demography
  - Diarrhea may occur in travellers from and to just about anywhere
  - "High risk" areas (diarrhea in > 30% of travellers)
    - Asia (but not Singapore)
    - Africa (but not South Africa)
    - Mexico
    - Central / South America
  - About half of all persons traveling from a "have" to a "have not" country will develop diarrhea
  - TD usually begins within 4 days to 14 days, and lasts
    - Usually < 1 wk
    - > 1 wk in ~10%
    - > 1 month in ~2%
  - For epidemiological purposes, TD may be subclassified as mild, moderate, or "classic":

	# unformed stools per day	Associated symptoms*
Mild	1-2	0
Moderate	> 2	0
	1-2	≥ 1
Classic	3 or more	≥ 1

*associated symptoms (in addition to diarrhea) include: fever, bloody stools, nausea / vomiting, abdominal pain

- Microbiology

- Give 15 of the major enteropathogens causing Traveller diarrhea.

No cause (idiopathic) is found in about half of cases.

- Bacteria
  - Enterotoxigenic Eschenchia coli (ETEC) – 90%
  - Enteropathogenic E. coli (EPEC)
  - Enteroaggregative E. coli (EAggEC)
  - Enteroinvasive E. coli (EIEC)
  - Salmonella

- Campylobacter jejuni
- Mycobacterium tuberculosis (and Mycobacterium bovis)
- Aeromonas and Plesiomonas

- Viruses
  - Rotavirus
  - Enteric adenoviruses (types 40, 41)
  - Measles virus
  - Human immunodeficiency virus

- Protozoa
  - Ciliophora
    - Balantidium coli
  - Mastigophora
    - Giardia lamblia
  - Coccidia
    - Cryptosporidium parvum
    - Isosprora belli
  - Microspora
    - Enterocytozoon bieneusi
    - Encephalitozoon intestinalis
  - Cyclospora – Cyclospora cayetanensis

- Helminths
  - Strongyloides stercoralis
    - Schistosoma

Printed with permission: Farthing, Michael J.G. Tropical *Sleisenger & Fordtran's gastrointestinal and liver disease: Pathophysiology/ Diagnosis/Management* 2006*:* pg 2308.

Clinical Pearl

- Diarrhea in the traveller is not always an infection – don't forget food intolerances, alcohol and drugs.

- Give 5 foods and/or beverages which are generally safe, often safe and often unsafe with respect to the risk for developing Traveller diarrhea.

Generally safe	Often safe	Often unsafe
○ Food and beverages served steaming (>59°C) hot ○ Bottled carbonated drinks including soft drinks and beer ○ Bottled water with intact seal apparent on opening ○ Syrups, jellies, jams, honey ○ Fruits that are peeled ○ Dry items such as bread an rolls ○ Any foods carefully prepared in one's own apartment or hotel	- Tortillas and breads or toast containing butter or sauces - Fruit juices which may have been augmented with tap water - Use of tap water to rinse mouth and toothbrush without swallowing it - Foods serviced on airplanes in developing regions - Few ice cubes	▪ Fruits and vegetables with intact skins: berries, tomatoes ▪ Hot sauces on tabletop ▪ Moist foods served at room temperature including vegetables and meats ▪ Any food served buffet-style that is maintained at room temperature ▪ Tap water even at hotels claiming filtration systems ▪ Large quantities of ice ▪ Hamburgers not served hot or at fast food service restaurants with rapid turnover of prepared hamburgers

Printed with permission: Dupont H.L. *Aliment Pharmacol Ther* 2008; 27: pg. 744.

➢ Treatment

"going prepared means eating and drinking wisely" (from a "Million-Miler Traveler")

➢ Prevention

- Helpful hints
  - Travel with the protection of health, cancellation and return-home insurance
  - Read the fine print: not all policies include persons with a "pre-existing condition"
  - Make sure the travel policy includes return of an accompanying person, such as your partner or RN
  - Ask your home physician to provide a typed summary of your medical condition, including a list of your medication and allergies.

- The immune compromised person with diarrhea
  - This includes many considerations, such as
    - The immune suppressed IBD or AIH patient
    - Organ transplantation
    - HIV infection
    - Chemotherapy
    - Diabetes
  - In the HIV-infected patient with CD4 counts < 200 cells / mm^3, chronic diarrhea may be due to
    - Enteric infections (including infections not common in non-immune-suppressed persons)
    - Drugs for HAART e.g.
      - Nelfinavir
      - Ritonavir
    - Infiltration
      - Lymphoma
      - Kaposi sarcoma
    - Non-HIV related etiologies
- Intake
  - Food
    - Eat only fruits or vegetables than can be peeled
    - Stay away from
      - Bottled sauces
      - Salts
      - Buffets
      - Ice cubes
      - Street vendors
  - Drink: wisely
    - Carbonated bottled water
    - Drinking straws
  - Remember
    - If the washroom in a restaurant is not clean, then (as a cautious general rule) the kitchen probably is not clean
    - Just because you wash your hands before eating does mean that food handlers wash their hands.

- Pretravel vaccination
- Prophylactic Antibiotics
  - "Rule of thumb" – use prophylactic antibiotics if you can't afford to be sick for 2 days
  - Co-morbid conditions
    - Severe heart, lung, kidney, GI / liver conditions
    - Transplantation recipients
  - "When being sick with diarrhea for a couple of days would be inconvenient" – it is up to you to decide what is "inconvenient"
  - Self-medicated, empiric antibiotics for treatment of TD
    - Ciprofloxacin 500 mg po bid, for 1 day to 3 days
    - Norfloxacin 400 mg po bid, or 1 day to 3 days
    - Azithromycin 1000 mg po, given once
    - Levofloxacin 500 mg po, given once
    - Bismuth subsalicylate 4 tabs (0 mL) po q 30 min until diarrhea stops; maximum 8 doses (concern for salicylate toxicity).
    - Ritaximin, 75% effective
- Note:
  - Azithromycin is preferred to
    - A quinolone in quinolone-resistant areas of the world, such as South East Asia e.g. Thailand
    - TMP-SMX (trimethoprim-sulfamethoxazole) in many parts of the world
  - Give azithromycin rather than a quinolone to <u>children</u>
  - Clinical resolution of symptoms does not always correlate with the loss of infectious agent in the stool (microbiologic eradication)

- Anti-diarrheal agents
  - Use cautiously
  - May possibly prolong the underlying infection
  - For non-bloody diarrhea
  - Only in conjunction with antibiotics

Clinical Caution – again

- EHEC
  - No antibiotics
  - No antidiarrheals (loperamide, diphenoxylate)
  - Antidiarrheals, antibiotics in EHEC → HUS, TTP
- C. difficile
  - No antidiarrheals → toxic megacolon

Abbreviations: TTP, thrombocytopenic thrombotic purpura; HUS, hemolytic uremic syndrome; EHEC (O157: H7), Enterohemorrhagic Escheichia coli); ETEC, enterotoxigenic E. Coli

- Give causes of prolonged diarrheal illness after travel ("**prolonged traveller's diarrhea**").
  - Infection
    - Persistent original bacterial infection
    - Missed second infection
    - Aeromonas
    - Escherichia coli (enteroinvasive)
    - Persistent protozoal infection
    - Giardia
    - Entamoeba histolytica
    - Cryptosporidium
    - Antibiotic-associated diarrhea (AAD), Cl. difficile infection
    - Onset of chronic (presumably viral) enteritis/colitis
  - Diet/Drugs
    - Change in diet
    - Excess alcohol intake
    - Drugs
  - Other Diseases
    - "Unmasked" lactase deficiency
    - Celiac disease
    - GSE
    - IBD
    - Microscopic (lymphocytic/collagenous) colitis
    - Tropical sprue
    - Post-infectious diarrhea-predominant IBS (D-IBS)

Abbreviations: AAD, antibiotic-associated diarrhea; D-IBS, diarrhea-predominant IBS; GSE, gluten sensitive enteropathy; IBD, inflammatory bowel disease.

Please see Feldman M., et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. Saunders/Elsevier, Philadelphia, 2010, Table 107.14, page 1873, "Relative Frequencies Microbial Causes of Traveller's Diarrhea"; Table 107.16, page 1875 "Drugs Used to Prevent Traveller's Diarrhea in Adults", and Table 107.17, "cause of Prolonged Diarrheal Illness After Travel".

Clinical Gems

- In the patient with suspected TD and with continued GI symptoms despite appropriate treatment and negative stool cultures, remember to consider
  - Post-infectious IBS (irritable bowel syndrome)
  - If travel was to a high risk area within a band 30^{o} latitude North and South of the equator, and consider tropical sprue
  - If the person lived for at least 1 month in the high risk area
  - Unrelated conditions, e.g. gluten sensitive enteropathy, colorectal cancer, SIBO (small intestinal bacterial overgrowth) bile salt wasting-associated diarrhea, lactase deficiency

"Education is the kindling of a flame,
not the filling of a vessel."

Socrates

SO YOU WANT TO BE A GASTROENTEROLOGIST!

A patient with chronic non-bloody diarrhea has an abdominal diagnostic imaging study which reveals hepatosplenomegaly and lymphadenopathy.

- Give the diagnostic considerations suggested by these imaging findings.
  - Infection
    - MAC
    - TB
    - Histoplasmomosis
  - Infiltration
    - Lymphoma
    - Metastatic disease
      - Adenocarcinoma
      - NET (neuroendocrine tumor)

Salmonellosis

- Give 6 conditions which predispose to Salmonellosis
  - Achlorhydria
  - Hemolytic anemia
  - Immunosuppression
  - Malignancy
  - Schistosomiasis
  - Ulcerative colitis

Please see Feldman M., et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. Saunders/Elsevier, Philadelphia, 2010, Table 107.9, page 1862 "Conditions that Predisposing to Salmonella Infection".

- Give the 5 clinical syndromes seen with Salmonella.
  - Gastroenteritis
  - Bacteremia
  - Typhoid fever
  - Localized infection
  - Carrier stage

Please see Feldman M., et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. Saunders/Elsevier, Philadelphia, 2010, Table 107.10, page 1863, Relative Frequency of the Clinical Syndromes of Salmonella Infection; Table 107.11, page 1864, "Infections for Antibiotic Therapy in Salmonella Gastroenteritis", and Table 107.12, page 1865 "Antibiotic Therapy for Bacterial Enteropathogens in Adults".

Clostridium Difficile Infection (CDI)

- Nosocomial (hospital-acquired)
- Community-acquired

Antibiotic-Associated Diarrhea (AAD), Pseudomembranous Enterocolitis (PMEC) and Clostridium difficile-Associated Diarrhea and Colitis (CDADC).

- Terms
  - There is overlap between AAD, PMEC and CDADC
  - PMC (pseudomembraneous colitis) or PME (pseudomembraneous enteritis)
    - The pseudomembrane is comprised of inflammatory and cellular debris
    - May be seen only on biopsy and not on colonoscopy
    - May be associated with underlying ulceration
    - May be only in R. colon (20%)
- Organisms
  - PMEC (PMC and PME) is caused by non-invasive C. difficile, S. aureus, and non-infectious conditions such as the seriously ill ICU patient.
- Predisposition
  - Predisposition to C. difficile indicates
    - Recent use of antibiotics, PPI
    - Antineoplastic chemotherapy
    - HIV
    - IBD (even in the absence of use of antibiotics)
    - Postpartum
  - PMEC
    - May develop in health community dwellers

- Poor hygiene
  - Dirty hospitals
  - Dirty hands

- Diagnosis
  - Diagnostic tests include
    - Tissue culture cytotoxicity assay
    - EIA (enzyme-linked Immunoassays) for toxin A and B
    - Culture followed by testing for toxin A and B
    - PCR (polymerase chain reaction) to detect the genes for the toxins
    - Colonoscopy: AAD plus PMC = C. diffcile colitis (sigmoidoscopy is not adequate, since 20% of PMC involves only the right side of the colon)
    - Another watch out: A normal colonic mucosa on sigmoidoscopy does **not** exclude C. difficile infection beyond the reach of the scope, in the colon or small intestine
- Clinical
  - ~20% of C. difficle diarrhea patients recur after initially successful treatment with metronidaazole or vancomycin. Because post-infectious IBS (irritable bowel syndrome) may present with similar symptoms, reculture is appropriate.

- Treatment
  - Acute attack
    - Metrodinazole, or vancomycin po
  - Recurrent C.difficile infection
    - Antibiotics
      - Repeat courses of metronidazole or vancomycin
      - Pulsed doses of vancomycin
      - Prolonged doses of vancomycin
      - Rifaximin
      - Cholestyramine or colestipol binding resins
      - Probiotics
      - IV pooled human immunoglobulin
      - Fecal transplantation

- General
  - Stop offending antibiotics
  - Contact precaution, especially hand hygiene
  - Supportive therapy

- Mild disease
  - General management
  - Stop offending antibiotics
  - Contact precaution, especially hand hygiene
  - Supportive therapy
  - Treatment options for recurrent C. difficile infections include
    - Repeat causes of metronidazole or vancomycin
    - Pulsed dose of vancomycin
    - Prolonged doses of vancomycin
  - Antibiotics (bacteriostatic)
    - Metronidazole 500 mg po tid, or 250 mg po qid, for 10 to 14 days
    - If metronidazole ineffective and symptoms persist, vancomycin 125 mg po qid, for 10 to 14 days
    - If patient requires antibiotics for non- C. Difficile indication, continue metronidazole or vancomycin ("concomitant antibiotics") for 1 week after other antibiotics for non- C. difficile infection is stopped.
    - Note; Risk of VRE (ancomycin-resistant enterococci) is similar with both metronidazole and vancomycin.
- Repeat vancomycin or metronidazole (usual treatment)
- Associations with metronidazole failures
  - Transfer from another hospital
  - CDI on hospital admission
  - Recent use of cephalosporin
- Intermittent (pulse) therapy
  - Antibiotic-free interval allows C. difficile spores to germinate, and be susceptible to being destroyed by next interval dose of antibiotic
- Tapered vancomycin

- Repeat stool cultures
  - Not indicated if symptoms subsided (50% will have C. difficile spores for up to 6 weeks in persons who have become asymptomatic)
  - Not indicated to treat C. difficle spore; even if person is toxin-positive, they may be an asymptomatic carrier.
- Recurrent CDI
  - Vancomycin given PO or PR (by enema) is absorbed through the inflamed colonic mucosa in CDI, so you must monitor serum creatinine for renal toxicity.
  - Recurrence of symptoms
    - 25% of persons treated with metronidazole or vancomycin
    - Recurrence usually within 3 weeks to 12 weeks
    - Of these with 1 recurrence, at least 25% will have a second recurrence
    - ½ due to relapse from original strain of C. difficile
    - ½ due to reinfection with a different strain

- Give 3 risk factors for recurrent CDI.
  - Age > 65 years
  - Need for concomitant antibiotics (antidote for medical condition, plus antibiotic for CDI)
  - Co-morbidities
  - ↓ host immune response (low anti-toxin antibody levels
  - Exposure to asymptomatic carriers

Note: Answering development of antibiotic resistance is not correct recurrence of CDI after initial treatment with metronidazole does not signify metronidazole resistance.

- Recurrence rates
  - Usual treatment, 31%
  - Pulse therapy, 14%
  - Taper regimen, 45%

- Sequential therapy
  - Vancomycin, followed by rifaximin for 14 days (88% response) previous exposure to rifaximin may cause rifaximin resistant C. difficile infection
- Anion-binding resins
  - Adjuvant therapy with tapered vancomycin
  - Cholestyramine or colestipol
- Intermittent (pulse) therapy
  - Antibiotic-free interval allows C. difficile spores to germinate, and be susceptible to being destroyed by next interval dose of antibiotic
- Tapered vancomycin
  - Sequential therapy
    - Vancomycin, followed rifaximin for 14 days (88% response) previous exposure to rifaximin may cause rifaximin resistant C. difficile infection
  - Fidaxomicin (bactericidal)
    - 200 mg po bid for 10 to 14 days

Response	FID	VANC
Acute (FD axomicin [FID] vs Vancomycin [VANC]	FID	= VANC
	10%	28%

May be optimal or patients with high risk of recurrence

- Probiotics (inconclusive results)
- Immunotherapy
  - Monoclonal antibodies (MAb)
    - Adjuvant to antibiotics (Ab), to reduce rate of recurrence

	Ab + MAb	Ab
Rate of recurrence	7%	25%

  - IVIG (intravenous immunoglobulin) – no proven therapy

- Fecal transplantation
  - Transplantation of stool (fecal bacteriotherapy, aka fecal microbiota transplantation)

Clinical Caution

Vancomycin given PO or PR (by enema) is absorbed through the inflamed colonic mucosa in CDI, so you must **monitor** serum creatinine for renal toxicity.

- Give the treatment of severe CDI (C. difficile infection).

➢ Severe CDI

- Scoring system
  - One point each for
    - Age 60 years
    - Fever > 38.3 ^{o}C
    - WBC > 15,000 WBC/μL within 48 hours of disease onset
    - Serum albumin < 2.5 mg/dL
  - Two points each for
    - PMC (pseudomembranous colitis) on endoscopy
    - Admission to ICU
  - Severe disease ≥ 2 points
  - Note
    - Some authorities include serum creatinine ≥ 1.5 x preinfection lever
- Complications
  - Patient
    - Shock
    - Death (within 30 days)
  - Colon
    - Megacolon
    - Perforation
    - Need for colectomy
  - Risk of complications for the hypervirulent stain of C. difficile, NAP (north American Pulsed Field type I), 11%
- Treatment
  - Vancomycin 125 mg po qid
  - For severe disease, vancomycin (VAN) is superior to metronidazole (Met)

	VAN	MET
Cure rate for severe CDI	97%	76%

- If patient with severe CDI is NPO (such as with megacolon or ileus), consider use of
  - Vancomycin by enema, 500 mg in 100 mL normal saline q 8 hour
  - Adding metronidazole 500 mg IV q 8 hour

- Surgery:
  - Indications
    - Worsening of patient
      - age ≥ 65 years
      - SIRA (systemic inflammatory response syndrome)
      - Multiorgan failure
      - Peritoneal signs
    - Colon
      - Megacolon
      - Severe ileus
      - Microperforation
      - Necrotizing colitis
    - Laboratory
      - WBC ≥ 20,000 WBC / μL, and / or
      - Plasma lactate, between 2.2 and 4.9 mEq/L
  - Procedures
    - Subtotal colectomy and ileostomy, secondary closure of ileostomy with ileorectal anastomosis
    - Diverting loop ileostomy, and colonic lavage (intraoperative PEG solution; post-operative autograge flushes of vancomycin into the ileostomy
- Transplantation of stool (fecal bacteriotherapy, aka fecal microbiota transplantation)

Clinical Caution

- Recurrence of symptoms after treatment for initial CDI does not automatically mean disease related to CDI, even if stool cultures are positive by stool toxin assay.
- This is because the patient may be an asymptomatic C. difficile carrier.

Giardiasis

- Flagellated protozoan parasite
- Source
  - Water
  - Food
- Common in
  - Day cares
  - Travellers
  - Campers
- Types
  - Sporatic
  - Epidemic
- Complications
  - Acquired lactase deficiency causing lactose intolerance for weeks to months
- Treatment
  - Contact precautions
  - Hand washing with soap (hand sanitizer kills the trophozoites but not the cysts)
  - Symptomatic persons
  - Asymptomatic carriers
    - Food handlers
    - Household contact of pregnant woman
    - Immune deficiency
    - Child or worker in daycare setting
  - Numerous drug options for first line therapy
    - Tinidazole
      - Patients > 3 yr of age
      - 50 mg / kg po od, 1 dose, with food
      - 1 dose > 90% efficacy
      - In pregnancy, use after first trimester
    - Metronidazole 15 mg/kg po per day, for 5 days
      - Efficacy 75% to 100%
      - AEs in ~ 25%
      - Avoid alcohol (disulfiram-like adverse effect)
    - Nitazoxanide
      - Patients > 1 year
      - Efficacy ~ 80%
      - Also active against cryptosporidium amebiasis

- Albendazole
  - Also effective against helminthes
- Mebendazole
  - Efficacy 80% to 100%
  - Take with food
- Paromomycin
  - Efficacy, ~55% to 90%
  - Poor absorption
  - Use in pregnancy

- Recurrence of symptoms after initial treatment of giardiasis
  - Assess
    - Associated immunodeficiency
    - Possible acquired lactose intolerance
    - Drug resistance
    - Recurrence of infection
      - Repeat stool testing for giardiasis
    - Continued duodenal inflammation
  - Treatment options
    - Repeat initial drug but use for longer, e.g. 5 days → 10 days
      - Higher dose
    - Use a different drug, or a drug from a different class
    - Combination therapy

Unless specially trained and experienced in the treatment of the following infections, it is recommended to consult a tropical diseases expert, or the CDA (Centers for Disease Control) and prevention drug service, Atlanta GA 30333, when faced with the management of the following.

www.cdc.gov/ncidod/srp/drugs/formulary.html
e-mail parasites@cdc.gov
phone: 1-404-639-3670

- **Protozoa**
  - Cyclospora cayetanensis
  - Isospora belli (now called Cystoisospora belli)
  - Cryptosporidium
  - Toxoplasma
  - Sarcocystis

Cyclospora

- Intracellular parasite
- Food and waterborne
- Not spread directly person-to-person
- Human are the only natural hosts
- Shed in a non-infective form
- Several days needed before the non-infective form becomes infectious
- Highly infectious attack rate, 92%
- Spectrum
  - Asymptomatic
  - Mild / severe disease
  - Acute or chronic
  - Non-specific small bowel mucosal biopsy changes
  - May be associated with acalculous cholecystitis
- Detect in stool by
  - Acid-fast staining of cryptosporidium
  - Fluorescent microscopy auto-fluorescent cyclospora oocysts
- Treatment
  - Immunocompetent TMP-SMX double-strength po 1 tab bid, for 7 day to 10 days
  - Immunodefecient TMP-SMX double-strength po 1 tab qid, for 3 wk to 4 wk
  - Maintenance TMP-SMX double strength po 1 tab tiw maintenance represents secondary prophylaxis
  - Alternate choice
    - Cipro' 500 mg po bid, for 7 days

Abbreviations: tiw, three times a week

- Cystoisospora belli (formerly called Isospora belli)
  - Mild, self-limited disease
    - TMX-SMX double strength po bid, for 7 days to 10 days
  - Severe disease (e.g HIV-co-infection)
    - TMX-SMX double strength po qid for 1 wk, then bid for 3 wks
    - Followed by maintenance therapy (secondary prophylaxis)
  - Life-threatening disease
    - TMP-SMX IV

- Alternatives
  - Cipro' 500 mg po bid for sulfa allergy or TMX-SMX non-responders
  - Other choice
    - Pyrimethamine po 75 mg per day for 4 wk, then 25 mg/day maintenance plus
    - Leucovorin 5 mg to 10 mg per day acutely and chronically (to prevent pyrimethamine-associated toxicity) or
    - Sulfadoxine 500 mg po, once a wk
    - Nitazoxanide

Helminthic Parasites

- Scabies
- Ascaris
- Trihuris
- Enterobius
- Note: treatments may need to be repeated
  - Contraindication not recommended for pregnant or lactating mothers
  - Not effective against hookworm infestation

- Treatment
  - Onchocerca volvulus
    - Ivermectin 100 mcg to 200 mcg per kg po, 1 dose
  - Strongyloidiasis
    - Ivermectin 100 mcg to 200 mcg per kg, 1 dose
    - Individuals, immune competent
  - Lymphatic filariasis
    - Ivermectin 100 mcg to 400 mcg per kg po, 1 dose, immunodeficient: above dose for 7 days, then repeat in 4 wks
    - Endemic areas, use ivermectin plus albendazole

- Albendazole
  - Echinococcus granulosis (cystic hydatid disease) given before surgical resection
  - 400 mg po, given with a fatty meal
  - Neurocysticercosis Taenca solium
  - Ascaris
  - Trichuris
  - Hookworm
- Other Benzimidazoles
  - Mebendazole
  - Thiabendazole
  - Triclabendazole

MCQ Alert: "Buzzwords"

Associations in the patient with diarrhea (multiple choice questions [MCQ])

Phrase	Think of
Nasal polyps, nail bed clubbing, dyspnea	– Cystic fibrosis
Middle aged male with MSK symptoms, pleurisy or pericarditis	– Whipple disease
Travel to India or Puerto Rico, low serum folate and B12	– Tropical sprue
Small bowel resection – Short – Long	– Bile acid-induced – Short bowel syndrome
Low serum iron and B12, high serum folate	– SIBO
Camping in Banff (Alberta)	– Giardiasis

Abbreviation: SIBO, small intestinal bacterial overgrowth; MSK, musculoskeletal system; DH, dermatitis herpetiformis; PPI, proton pump inhibitor

More MCQ Alert: "Buzzwords"

Associations in the patient with diarrhea (multiple choice questions [MCQs])

Phrase	Think of
○ Enteritis + acid-fast staining	– TB – MAC – Isospora belli – Cryptosporidium
○ HIV-associated diarrhea	– Haiti – Charcot Leyden crystals in stool
○ Foamy macrophage on small bowel biopsy	– MAC – Tropheryma Whippelii
○ Abdominal pain plus	– Mediterranean origin ▪ FMF (Familial Mediterranean Fever) ▪ IPSID (immunoproliferative small intestinal disease)
○ Perianal disease, smoking	– Crohn disease
○ Irish, DH, iron deficiency	– Celiac disease
○ Immune suppressed	– Enteric infection
○ Dyspepsia treated with PPI	– Drug-induced, microscopic colitis, C. diff
○ Holiday in Mexico	– Traveller's diarrhea
○ Eating – Hamburger – Rice – Whipped cream	 – E. Coli O157:H7 – Staph. Toxin
○ Gastric surgery	– Dumping syndrome
○ Alcohol consumption	– Direct effect ▪ Lactose ▪ Pancreatic insufficiency

SMALL INTESTINAL BACTERIAL OVERGROWTH SYNDROME (SIBO)

- Give the usual bacterial presence (10^x/mL) of different sites along the gastrointestinal tract.
  - Stomach – 10^3/mL
  - Jejunum – 10^4/mL
  - Ileum – 10^{6-8}/mL (gram-positive)
  - Colon – 10^{10-12}/mL (gram-negative, anaerobic, facultative aerobic)

*note that **> 10^5/mL** in the proximal small intestine is considered to be abnormal, and is compatible with the **diagnosis** of SBBO.

Secretory IgA is the predominant immunoglobulin found in intestinal secretions.

- Give two functions of Secretory IgA.
  - Binds bacteria and dietary antigens (thus limiting absorption/immune response)
  - Phagocytosis

- Give the immunologic characteristic makes this immunoglobulin ideal for its function in the GI tract?
  - Resistant to digestion
  - Secreted
  - Does not activate complement cascade
  - Does not participate in antibody-dependent cytotoxicity.

- Give 3 conditions associated with immunoglobulin deficiency.
  - Isolated IgA deficiency
    - Giardiasis
    - False-negative testing for celiac disease using IgA transglutaminase antibiotic
  - CVI (common variable deficiency)
    - Gastric adenocarcinoma
    - Intestinal lymphoma
    - Non-Hodgkin lymphoma

- Give 8 components of the GI mucosal barrier, and for each give their function to protect against enteric infection.

Components	Function
○ Epithelium: glycocalyx, villi	– Innate immune response – Antigen presentation – Block penetration of ingested antigens (tight junctions)
○ Defensins	– Antimicrobial peptides
○ Trefoil factors	– Protection from a variety of deleterious agents (bacterial toxins, chemicals and drugs); provide restitution after mucosal injury
○ Mucus/mucins	– Block penetration of ingested antigens
○ Proteases: pepsins, pancreatic enzymes	– Breakdown of ingested antigens
○ Gastric acid (pH)	– Breakdown of ingested antigen
○ Bile acids	– Breakdown of ingested antigens
○ Intestinal peristalsis	– Block penetration of ingested antigens
○ Indigenous microflora (microbiotica)	– Competitive inhibition – *Direct:* competition for essential nutrients and bacterial receptor sites; creation of restrictive physiological environments; secretion of antibiotic-like substances – *Indirect:* chemical modification of bile salts and dietary fats, induction of protective Ig responses, stimulation of peristalsis
○ Secretory-IgA (s-IgA)	– Binds bacteria and dietary antigens – Phagocytosis
○ GALT-associated IgA, IgG, IgM (serum)	– Clear antigens penetrating gastrointestinal barrier/systemic immunity – Assist in opsonization and phagocytosis of antigens
○ Lymphoid follicles in lamina propria	– Clear antigens penetrating gastrointestinal barrier
○ Intraepithelial lymphocytes (IEL)	– Innate and acquired immune responses
○ Mesenteric lymph nodes	– Phagocytosis and antigen presentation

Printed with permission: Acheson DWK. *Best Pract Res Clin Gastroenterol* 2004;18(2):pp 389

- Give 15 conditions that cause or are associated with small intestinal bacterial overgrowth.
  - Reduced gastric acid
    - Atrophic gastritis, pernicious anemia
    - Medications (H2 receptor antagonists, proton-pump inhibitors)
    - Gastric surgery
  - Reduced pancreatic and biliary secretion
    - Pancreatic insufficiency
    - Cholestasis
  - Structural abnormalities (neoresevoirs, fistulae)
    - Small bowel diverticulae (not colonic diverticulae)
    - Adhesions
    - Surgical anastomosis and diversions
    - Fistulae (colo-enteric, gastrocolonic)
    - Strictures, webs
    - Absent or incompetent ileocecal valve
  - Dysmotility syndromes
    - Diabetes
    - Drugs
    - Acute enteric infection
    - Scleroderma
    - Intestinal pseudo-obstruction syndromes
    - IBS-D association, IBS-C association
  - Decreased host defense (decreased immune function)
    - Undernutrition
    - Immune deficiencies particularly absence of secretory immunoglobulin A (IgA)

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- Give the mechanism by which signals from particulate and microbial antigens related to the pathogenicity of luminal microbiota are converged to the intestinal immune system.

  - M cells and mucosal dendritic cells
    - Sampling: TLR (Toll-like receptors, a type of pattern recognition receptor)
    - Signaling; NFkB signals proinflammatory responses

Please see Feldman M., et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. Saunders/Elsevier, Philadelphia, 2010, Table 102.1, page 1992, "Examples of metabolic activities of intestinal microbiota".

- Laboratory

SO YOU WANT TO BE A GASTROENTEROLOGIST!

The serum concentration of vitamin B12 may be reduced from bacterial uptake and consumption of dietary cobalamine), but serum levels usually are normal. In tropical sprue there may be co-infection with facultative anaerobic,and toxigenic coliforms, but in these patients with bacterial overgrowth in the small intestine, the serum or RBC folate levels are reduced.

- Give the explanation for the reduced RBC / serum folate concentrations in SIBO (small intestinal bacterial overgrowth) associated with tropical sprue, but not in SIBO associated with Crohn disease.
  - The luminal contaminating organisms in SIBO produce folate, which is absorbed in the patient with SIBO, resulting in normal or even increased blood levels.
  - In contrast, in tropical sprue, the contamination is with facultative anaerobes, toxigenic coliforms, which take up and use folic acid, depriving the host patient of folic acid, and leading to folic acid deficiency.

- Give 5 tests to diagnose small intestinal bacterial overgrowth (SIBO), and give the principal of their use.
    - Jejunal aspiration ($>10^5$/mL)
    - Jejunal luminal bile acids (deconjugated and dehydroxylated)
    - H2 – breath test with lactulose
    - C^{13} glycocholic acid, D-xylose
    - Schilling test
    - Trial of appropriate antibiotic

Abbreviation: SIBO, small intestinal bacterial overgrowth syndrome

- Treatment
    - Correct any predisposing condition, if possible
    - Nutrition (correction of SIBO complications)
        - Lactose-free, low-residue diet
        - Increase calories/ protein if malnourished
        - Micronutrient supplementation -vitamin B12, fat soluble vitamins (A, D, E and K), iron, calcium, magnesium, zinc
    - Drugs
        - Antibiotics versus (gram-neg anaerobes) e.g., metronidazole, tertracycline (**not** in children), cipro' (**not** in pregnancy), prebiotics, probiotics
        - Prokinetics
        - Interval or maintenance therapy, where appropriate

Abbreviation: SIBO, small intestinal bacterial overgrowth syndrome

MCQ Caution

The diagnosis of SIBO cannot be made from stool cultures

"To be gentle, tolerant, wise and reasonable
requires a goodly portion of toughness."

Peter Ustinov

CELIAC DISEASE

- Give 20 intestinal and extraintestinal conditions associated with celiac disease.

- Intestinal
    - Esophagus – squamous cell Ca, adenocarcinoma, eosinophilic esophagitis
    - Stomach – lymphocytic gastritis; pernicious anemia, atrophic gastritis
    - Small bowel
        - Celiac disease (classical, silent, potential)
        - Collagenous sprue
        - Ulcerative ileojejunitis
        - Necrotizing mesenteric lymphadenopathy
        - Diffuse small intestinal lymphoma (T- or B-cell)
        - Non-responsive celiac disease (NRCP, primary [1º] or secondary [2º]
        - Refractory sprue, types 1 and 2
        - Early aberrant T-cell lymphoma (EATL)
        - Unclassified sprue (sprue-like intestinal disease)
        - SIBO
        - Adenocarcinoma
    - In Europe, the standard mortality rate of persons with symptomatic celiac disease is increased and varies from 1.26 in Finland to 3.6 in Sicily (Biagi & Corazza, 2010).
    - Colon – microscopic colitis, IBS
    - Liver
        - Autoimmune hepatitis (AIH)
        - Autoimmune cholangitis (AIC)
        - Primary biliary cirrhosis (PBC)
        - Primary sclerosing cholangitis (PSC)
        - Ideopathic transaminitis
        - Fatty liver

- Pancreas
  - 1^{o} unmasked non-related pancreatic deficiency
  - 2° insufficiency (↓ stimulated relapse of CCK, no intrinsic pancreatic disease)
  - Diabetes
  - Autoimmune pancreatitis
- Nutritional abnormalities - short stature, osteopenic bone disease, iron and vitamin deficiencies, unexplained weight loss
- Growth failure may occur in children with undiagnosed celiac disease, and catch-up growth may be incomplete after introducing a gluten-free diet.

- Extra-intestinal
  - Neuropsychiatric and CNS
    - Chronic fatigue syndrome
    - Irritability, depression
    - Peripheral neuropathy
    - Epilepsy (with intracranial calcifications)
    - Gluten ataxia syndrome (gait and limb ataxia), paresthesia
    - Night blindness
    - Autism (controversial)
  - Teeth
    - Dental enamel defects
  - Lung
    - Fibrosing alveolitis
    - Bird fancier's lung
  - Hematopoietic
    - Iron deficiency anemia, hemorrhage, ↓ intake
    - Thromobocytosis
    - Howell-Jolly bodies
    - IgA deficiency
  - Musculoskeletal
    - Atrophy, tetany, weakness, myalgias, osteoporosis
    - Autoimmune connective tissue disorders: Sjorgren's syndrome, RA, lupus
    - Osteoporosis

- Endocrine - secondary hyperparathyroidism, insulin-dependent DM, (T, DM), autoimmune thyroid disease, autoimmune adrenal disease
- Integument
  - Follicular hyperkeratosis, dermatitis
  - Petechiae, ecchymoses
  - Dermatitis herpetiformis
  - Edema
  - Acrodermatitis enterohepatica
- Obstetrical - infertility, obstetrical complications (miscarriage), amenorrhea
- Renal – IgA nephropathy
- Miscellaneous - Downs syndrome, Turners syndrome
- Pediatrics - delayed puberty, slow growth

Abbreviations: AIC, autoimmune cholangitis; AIH, autoimmune hepatitis; CD, celiac disease; DM, diabetes mellitus; IBS, irritable bowel syndrome; PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis; RA, rheumatoid arthritis

Adapted from: Green PHR, et al. *Best Pract Res Clin Gastroenterol* 2005;19(3): pg 39.; and Crowe SE. *2007 AGA Institute Postgraduate Course*: pg. 25.

- Dermatitis Herpetiformis (DH)
  - Response to gluten withdrawal is seen in DH
  - These persons have type 3 tTG which leads to IgA precipitation in the papillary dermia.
  - A pruritic papulovascular rash is seen on extensor surfaces as well as on the buttocks, trunk, neck and scalp.
  - Biopsy of the skin lesions will show areas characteristic granular / speckled (90%) or linear (10%) deposits of IgA at the dermoapidermal junction.

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- In the context of IgA deposits around the skin lesion of persons with DH, give differences between linear IgA disease, and the usual granular / speckled IgA deposits around the skin lesion in DH.
  - Linear IgA disease occurs in ~10% of persons with DH-like papulovascular skin lesions, and this condition differs as follows from the normal DH with granular / speckle IgA deposits:
    - ↑ IgA anti-basement membrane antibody in blood
    - Absent tTG or EMA (endomyseal antibody)
    - HLA susceptibility genes other than HLA DQ2 or DQ8
    - No gluten-sensitive enteropathy

➢ Laboratory

- The HLA close II molecules DQ2 and DQ8 are required for but are not sufficient by themselves for the development of CD: 50% of Americans are positive for one of these molecules, but only 1% develop CD. However negative HLA DQ2 or DQ8 rule out CD as a cause of the enteropathy (high negative predictive value).
- IgA tTG (tissue transglutamase) serology is >95% sensitive for CD, especially when there is a high titre
- Anti-gliadin antibodies have a relatively high false negative rate, and have been replaced by IgG DPG (deamidated gliadin peptide) assays that have a sensitivity comparable to anti-tTG

The tTG serological test for CD may be falsely negative in celiac patients with selective IgA deficiency.

- Give three other conditions in which there may be an increased risk of selective IgA deficiency.
  - Pernicious anemia
  - Giardiasis
  - Secondary deficiency of disaccharidases

Treating isolated IgA deficiency with IgA is **not** recommended, because it is not required

- Give another reason why IV immunoglobulin should not be used to treat isolated IgA deficiency.
    - Persons with IgA deficiency may have IgG or IgE antibodies to the IgA in the IV immune globulin (anti-IgA antibodies), to which they could have a severe anaphylactic reaction.

- Give clinical indications for serological testing for CD.
    - Positive family history
    - Autoimmune endocrine disorders
        - Insulin-dependent diabetes mellitus
        - Autoimmune thyroid disease
        - Autoimmune adrenal disease
    - Autoimmune connective tissue disorders
        - Sjogren's syndrome
        - Rheumatoid arthritis
        - Systemic lupus erythematosus
    - Hepatobiliary conditions
        - Primary sclerosing cholangitis
        - Primary biliary cirrhosis
        - Autoimmune cholangitis
        - Elevated transaminases
    - Other gastrointestinal disorders
        - Lymphocytic gastritis
        - Microscopic colitis
    - Miscellaneous conditions
        - IgA deficiency, IgA nephropathy
        - Down syndrome, Turner's syndrome

Printed with permission: Crowe SE. *2007 AGA Institute Postgraduate Course*: pg. 25

- Diagnostic imaging
    - Dilation of small bowel lumen
    - Mucosal fold thickening
    - Flocculation of barium on small bowel on X-ray

- Endoscopy
  - The endoscopic features of CD (scalloping of the muscosal folds, less prominent folds, fissules, and a nodular/ mosaic pattern) are only 59% sensitive but 92% specific for CD
  - The rate of complete enteroscopy is three times higher with double than with single balloon enteroscopy (66% vs 22%) (May et al., 2010; 105: 575-81).

- Give 4 causes on EGD of duodenal scalloping other than celiac disease.

o Other "sprues"	– Tropical sprue
o Infections	– Giardiasis
	– HIV infection
	– Eosinophilic enteritis
o Systemic disease	– Amyloidosis

- Give 10 clinical conditions which are associated with **false positive** or **false negative**, serologic testing for CD.
  - False negative
    - True false negative
    - IgA deficiency
    - Children < 2 years
    - Recent gluten free diet
    - TPN (NPO, with no gluten taken by mouth)
    - Current or recent use of corticosteroids, immunosuppressives, anti-TNFs
    - Previous hematopoietic stem cell transplantation
  - False positive
    - Congestive heart failure (New York class 3 or 4)
    - Autoimmune diseases (may be associated with CD which is in a latent phase)
    - Liver diseases
    - Inflammatory bowel disease
    - Silent (occult), or potential (latent) celiac disease

Adapted from: Green PHR, et al. *Best Pract Res Clin Gastroenterol* 2005; 19(3): pg 391.

- Anti-pituitary antibodies (APA) is suggestive of autoimmune hypopituitorism (based on lymphocytic hypophysitis) occur in 42% of newly diagnosed celiac youths (30% high and 70% low titer of APA), and may also be associated with low level of IGF-1 (Devecchio et al, AJG 2010; 105: 691-6).

Anemia with ↑MCV (mean cell volume) occurs with deficiency of folic acid or vitamin B12.,

- Give the type of sprue which is likely the cause when ↑ MCV occurs with diarrhea, and the recommended treatment for each.
  - Laboratory
    - Celiac sprue
      - ↓ folic acid (common), ↓ B12 (rare)
    - Tropical sprue
      - ↓ folic acid
  - Treatment of
    - Celiac sprue
      - Lifetime gluten-free diet
    - Tropical sprue
      - Tetracycline 250 mg po qid, plus
      - Folic acid 5 mg po od

➢ Pathology

- Looks like colon, but if you see Brunner glands-must be duodenum.
- Note that in celiac disease the small bowel mucosal biopsy is compatible with the diagnosis, but is **not** pathognomic.

- Give conditions causing malabsorption that are usually excluded by a normal small bowel mucosal biopsy.
  - Sprue (actually, not always – patchy, treated, immunosuppression, latent or potential – anti tTG positive (latent), but small bowel biopsy histologically normal)
  - Hypogammaglobulinemia
  - α-β-Lipoproteinemia
  - Whipple disease (except in very rare circumstances with only CNS Whipples)

- Common errors
  - Very mild celiac
  - The subtle ↑ IELs (intraepithelial lymphocytes) is missed
  - Very severe celiac disease
  - 4 to 6 duodenal or jejunal mucosa biopsies is the correct answer, although beware
    - The mucosal biopsy may be compatible with celiac disease, but there are no features which are pathognomic

For the following conditions which may be associated with a "**sprue-like" lesion**, indicate the histological features which may be used to distinguish the condition from celiac disease.

Cause of malabsorption	Histological features
o Abeta-lipoproteinemia	- Large lipid droplets
o Amyloidosis	- Congo red-stained deposits with apple-green birefringence in polarized light
o Collagenous sprue	- Collagenous band below atrophic epithelium
o Crohn disease	- Epitheloid granulomas and characteristic focal inflammation
o Eosinophilic gastroenteritis	- Eosinophilic infiltration
o Infection	- Organism seen on histological examination (eg. giardia lamblia, strongyloides, TB, HIV)
o Lymphangiectasia	- Ectatic lymph vessels, fat in lymphatics
o Lymphoma	- Clonal expansion of lymphocytes
o Mastocytosis	- Diffuse infiltration with mast cells
o Mycobacterium-avium complex infection (MAC)	- Acid-fast bacilli, foam cells, PAS positive macrophages
o Whipple	- Acid-fast bacilli, foam cells, PAS positive, diastase resistant staining in macrophages

Abbreviation: MAC, mycobacterium-avium complex infection

Adapted from*:* Freeman HJ. *Can J Gastroenterol* 2008; 22(3): pg. 277.

- Treatment
  - A daily intake of <10 mg of gluten is unlikely to cause significant histological abnormalities (Akobeng AK and Thomas AG. Aliment Pharmacol Ther 2008; 27: 1044-1052.)
  - The patient with proven celiac disease (CD) must be on a gluten-free diet for life
  - Associated nutrient deficiencies are treated
  - Associated intestinal and non-intestinal conditions are anticipated and treated

- Give causes of diarrhea malabsorption with biopsy-demonstrated villous atrophy but normal numbers of IELs (villous shortening, N-IELs).
  - Variants of celiac disease
    - Non-responsive celiac disease (NRCP, 1º / 2º)
    - Refractory celiac (RCD)
    - Ulcerative jejunoileitis
    - EATL Type 1 or 2
    - Enteropathy-associated T-cell lymphoma
  - GI conditions
    - Radiation enteritis
    - Immunoproliferative small intestinal disease
    - Crohn disease
    - Eosinophilic gastroenteritis
    - Autoimmune enteropathy
    - Whipple disease
  - Infection
    - Tuberculosis (including atypical)
    - HIV/AIDS
  - Immunodeficiency
    - Common variable immunodeficiency syndrome
  - TPN
    - TPN (total parental nutrition)

Printed with permission: Daum S, Cellier C, Mulder CJJM. *Best Pract Res Clin Gastroenterol* 2005; 19(3): pg. 415.

- Non-responsive celiac disease (NRCD) is defined as "….. the persistence of symptoms, signs, or laboratory abnormalities typical of celiac disease despite adherence to a gluten-free diet for at least six months" (Feldman M., et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. Saunders/Elsevier, Philadelphia, 2010, page 1815).
- Primary NRCD
  - Non-responsive immediately after the initial diagnosis, so does not fulfil the above definition of NRCD, or for that matter does not fulfil the diagnosis of celiac disease.
- Secondary NRCD
  - Definition as above, but includes the concept of an initial response to a gluten-free diet (GFD), and then loss of this beneficial response
  - RCD type 2 associated with
    - Ulcerative jejunitis (UIJ)
    - UIJ may undergo
      - Malignant transfunction to diffuse or multifocal EATL (enteropathy-associated T cell lymphoma).
      - Necrotizing mesenteric lymphodenopathy

Refractory celiac disease (RCD) is symptomatic severe small intestinal villous atrophy mimicking celiac disease but does not respond to at least 6 months of a strict gluten-free diet and not accounted for by other causes of villous atrophy or overt intestinal lymphoma

- Type 1
  - IELs
    - Have the usual CD8 expression pattern CD8, CD4, IL-2R
    - Are phenotypically normal
  - 5-year mortality rate, 10%
  - No aberrant clonal changes
  - 5-year mortality rate, 10%
- Type 2
  - IELs are phenotypically abnormal
  - IELs lack the usual CD8 expression pattern
  - Aberrant clonal changes monoclonal rearrangement of the TCR and gene
  - ↑↑ IL-15 may be responsible for this lymphomatous transformation
  - 1 year mortality rate of ~70%

  - Despite nutritional support, steroids (including budesonide), immunosuppressants, anti-TNF or stem cell transplantation
  - A strict gluten-free diet for 5 to 10 years markedly reduces the risk of EALT as well as small bowel adenocarcinomas
- 10% of NRCP → RCD, 1% of CD → RCD
- After instituting a GFD, 90% of CD patients lose their symptoms and signs, and anti-tTG normalizes, even with low level or episodic intake of gluten
- 10% of CD patients develop 1˚ or 2˚ NRCD, sometimes (36%) due to non-adherance to the receommended GFD (36%)

***with unclassified sprue (or sprue-like intestinal disease), no initial response to a gluten-free diet was documented.*

Abbreviations: GFD, gluten free diet; IELs, intra-epithelial T cell lymphocytes; NRCD, non-responsive CD; RCD, refractory celiac disease

- Give the acceptable foods, and the foods to avoid for CD patients.

- Acceptable foods
  - Corn, rice, buckwheat products, potatoes
  - Wine, and distilled alcoholic beverages
  - Fruit and vegetables
  - Meat
  - Nuts
  - Dairy products (unless lactose-intolerant)

➢ Foods to avoid (please also see following question)
  - Wheat, rye, barley
  - Triticale (wheat-rye hybrid)
  - Millet and sorghum
  - Oat products (if there is cross-contamination)
  - Hydrolyzed vegetable protein
  - Beer, lager, stout, malt

- Give 10 common **sources of hidden gluten**.

➢ Foods and beverages
  - o Bouillon/soups
  - o Candy
  - o Communion wafers
  - o Contamination
  - o Drink mixes/herbal tea
  - o Fat replacers
  - o Gravy/sauces
  - o Imitation meat/seafood
  - o Malt alcohol/vinegar
  - o Nutritional supplements
  - o Salad dressings/marinades
  - o Self-basting turkeys
  - o Soy sauce

- A patient with previously well-controlled biopsy-proven CD while on a gluten-free diet (GFD), develops recurrent diarrhea, still while on a GFD.

- Give 15 causes or conditions specific to CD that could explain this clinical scenario.

  - o Diet
    - Non-adherence to GFD
    - Unintentional gluten intake
    - Zinc deficiency, folate/B12 deficiency
    - Primary lactose intolerance (lactase deficiency)
    - Severe malnutrition
  - o Intestinal complications of sprue
    - Refractory celiac disease*
    - Collagenous colitis
    - Small bowel adenocarcinomans
    - Early abberrant T cell lymphoma (EATL)
    - Lymphoma of small bowel
    - Ulcerative jejunoileitis
    - Lactose/fructose malabsorption

- Other GI complications of CD
  - Primary pancreatic deficiency
  - Loss of stimulus for pancreatic enzyme secretion; unmasked unrelated pancreatic insufficiency
  - Cholestatic liver disease
  - Small bacterial overgrowth (SIBO)
  - Diarrhea – predominant irritable bowel syndrome (IBS-D)
  - Microscopic colitis
  - Unclassified sprue
- Non-intestinal complications
  - Diabetes
  - Thyroid disease (hypo- [SIBO] or hyperthyroidism[rapid transit])
  - Adrenal insufficiency
- A second disease, or an incorrect initial diagnosis (including unclassified sprue**)

**refractory celiac disease requires evidence of an initial response to a gluten-free diet.*

Abbreviation: CD, celiac disease; EATL, early abberrant T cell lymphoma; GFD, gluten-free diet; IBS-D, predominant irritable bowel syndrome

Adapted from: Freeman HJ. *Can J Gastroenterol* 2008; 22(3): pg. 277.

TROPICAL SPRUE

- Definition
  - Common in a 30^{o} latitude north and south of the equator, but curiously less common in
    - Carabean
      - Jamaica
      - Bahamas
    - Asia
      - China
      - Middle East
  - Seen in permanent residents of these areas, as well as in travellers who have lived in the area for 2 wk to 4 wk

- Causes / assciations
  - Co-infections with toxigenic organisms
    - E.Coli
    - Enterobacter
    - Klebsiella

- Pathology
  - Small bowel mucosal biopsies (sprue-like)

- Diagnostic imaging: non-specific
  - Dilation of small bowel lumen
  - Mucosal fold thickening
  - Flocculation of barium on small bowel on X-ray

- Differential

A person with Caucasian ancestory who has lived in India for 2 years returns to their home in Northern England. While in India they developed diarrhea which was thought to be due to tropical sprue, so was treated with tetracycline 250 mg po qid for 3 months plus folic acid. Their small bowel biopsy is compatible with celiac disease, and their HLA DQ2 is positive.

- Give the manner in which celiac sprue can be distinguished from tropical sprue.
  - HLA-DQ2 or 8 are required in order for celiac disease to develop, but about 30% of healthy Caucasians are positive or HLA-DQ2 or 8, so this doesn't prove they have sprue, but the absence of HLA-DQ2 or 8 proves they don't have celiac disease.
    - Non-HLA-DQ2 or DQ8 celiac disease is rare, but is being reported.
  - Some persons with sprue-like symptoms and normal celiac serology will respond to a gluten-free diet; they are thought to have non-celiac gluten-sensitivity (NCGE).
  - The symptoms of tropical sprue may resolve spontaneously, and relapses / recurrences occur in about 20%, so the elapse of symptoms does not prove the original diagnosis of tropical sprue was incorrect.

- So how do you proceed? The key is to help the patient, to undertake measures which reduce symptoms and improve the quality of their life
  - Place the patient on a strict gluten-free diet for 6 months, and correct nutrient deficiencies (especially folic acid) as well as malnutrition
  - If the tTG level was initially increased and falls, as well as the symptoms improve greatly, continue the gluten-free diet.
  - If the tTG was initially normal and if the gluten-free diet failed to help the patient's symptoms, then give a retreatment course of antibiotics (e.g. tetracycline).
  - Don't forget that the patient could have another diagnosis such as SIBO, bile salt wastage, microscopic colitis; and don't forget screening colonoscopy.

- Treatment
  - Folic acid 1 mg to 5 mg po od, or 2 wk to 4 wk, without antibiotics, often resolves symptoms and signs
  - If vitamin B12 is deficient, correct; as well treat other deficiencies, such as protein / calorie malnutrition
  - If an antibiotic is necessary, it may be given by itself or with folic acid
  - Suggested antibiotics
    - Tetracycline 250 mg po qid, for 3 months to 6 months
    - Tetracycline cannot be used in
      - Children
      - Pregnant women
      - Tetracycline allergy
      - Alternative; Use a sulfonamide for 3 to 6 months

"Study without desire spoils the memory,
and it retains nothing that it takes in."

Leonardo da Vinci

WHIPPLE DISEASE

- Demography
  - Medium $4/10^7$ per year (rare)!

- Organism
  - Caused by chronic infection of Tropheryma whipplei, a rod-shaped bacterium
  - T. whipplei 16S rRNA is mortly extracellular, and below the basement membrane

- Pathology
  - The PAS (periodic acid-Schill)-positive, diastase resistant inclusions in the phagolysosomes of the "foamy" macrophage are filled with glycoprotein, possibly representing bacterial remnants of their cell walls.
  - ~ 25% have CNS infection, rarely without intestinal, joint or heart involvement, and CSF cytology and stereotactic biopsy of lesions shown MRI or CT scan may be necessary.

Whipple disease, a systemic infection caused by Tropheryma whipplei, has "foamy macrophages" in the submucosal of the small or large (rare) intestine, and these stain PAS-positive, diastase sensitive macrophage staining.

- Give 2 causes of PAS-positive sensitive macrophage staining.
  - MAC enteritis
  - A1AT alpha-1 anti-trypsin deficiency

- Pathophysiology
  - ↓ Th1 and ↑ Th2 immune response
  - ↑ IL-16 and nucleosomes (suggesting ↑ apoptosis) from macrophage and monocytes

- Clinical
  - 10% of Whipplei patients have secondary infection from Giardia lamblia.
  - Malabsorption pictures as well as lymphadenopathy (peripheral, mesenteric and retroperitoneal)

- Lipid droplets and lymphangiectasia are common in the small bowel, and the PAS-positive diastase-resistant material in the macrophage is glycoprotein.
- Lymphadenopathy
  - Peripheral – lymphadenitis
  - Abdominal – granulomatous reaction and fat deposits

- Give 3 "buzzwords" for tropheryma whipplei infection (Whipple disease) in addition to PAS-positive, diastase-resistant foamy macrophages.
  - Cerebellar ataxia plus diarrhea
  - Pericarditis, pleurisy in middle-aged male
  - Nystagmus plus oculomasticatory myorhythmia

➢ Diagnosis
- Performance characteristics of PCP analysis of saliva and stool: when both are positive, sensitive is 65% and specificity is 95% for intestinal involvement.

Clinical Challenge

A middle-aged male with malabsorption, arthralgias, pericarditis, peripheral lymphadenopathy and hyperpigmentation in sun-exposed areas of skin is suspected as having Whipple disease. CNS infection is common (~70%) in persons with GI Whipple disease.

- Give the common and characteristic CNS findings arising from perivascular infiltration with PAS-positive macrophage.
  - Common
    - Dementia (~60%)
    - Supranuclear ophthalmoplegia (~40%)
    - Altered LOC (level of consciousness)
  - Characteristic (in < 20% of Whipple patients)
    - Oculomasticating myorhythmia
    - Oculofacial skeletal myorhythmia

Please see Feldman M., et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. Saunders/Elsevier, Philadelphia, 2010, Table 106.1, page 1841 "Antibiotics used to treat Whipple's Disease".

- Treatment
  - Replace associated
    - Loss of fluid/ electrolytes
    - Nutrient deficiency
  - Treat associated giardiasis
  - Induction (10-14d)
    - Penicillin
      - Nonsensitive
        - Penicillin E 6-24 million µ IV od on divided doses plus
        - Streptomycin 1g imod
      - Sensitive
        - Ceftiaxome 2g IV od for 10-14d
  - Maintenenance (1yr)
    - Sulfa
      - Nonsensitive
        - TMP/SFX 160mg/800mg po bid
      - Sensitive
        - Rifampin 600mg od

You have enemies? Good.
That means you've stood up for something,
Sometime, in your life.

Winston Churchill

SHORT BOWEL SYNDROME (SBS)

SO YOU WANT TO BE A GASTROENTEROLOGIST!

A patient with a distal small bowel resection of > 200 cm develops **cholerhitic diarrhea** (bile salt-induced diarrhea). Giving the bile salt binding agent cholestyrame improved the watery diarrhea, but worsened the steatorrhea. Giving UDCA (ursodeoxycholic acid) worsened the steatorrhea.

- Give the therapeutic option which may prove to be useful in this situation, and give 3 **metabolic abnormalities** associated with the surgical resection which may be corrected by this therapy.

  - The synthetic conjugated bile acid cholylsarcosine may be beneficial
    - Watery diarrhea the cholylsarcosine does not undergo bacterial deconjugation, and thus has less effect on aggravating watery diarrhea.
    - The cholylsarcosine will assist in the solubilisation of lipids and their absorption, thereby improving the steatorrhea.
    - With the reduction in the steatorrhea, there will be less free fatty acids in the lumen, less absorption of dietary oxalate, less oxalate absorption, and fewer renal caliculi.
    - Some cholylsarcosine is absorbed and sufficient cholylsarcosine conjugated and secreted from the hepatocytes that the solubility of cholesterol in bile will not be surpassed will not become “lithogenic”, and thus there may be a lower risk for the development of cholelithiasis.

Some patients with SBS who are maintained nutritionally well on TPN may develop severe, progressive cholestatic liver disease, which may be lessened if the volume of TPN is reduced.

- Give the role of GLP-2 (Teduglutide) in the management of SBS.
  - Teduglutide is a long-acting synthetic homolog of GLP-2, which
    - Enhances the intestinal adaptive response following extensive small bowel resection
    - Can be given daily (SC) in persons with SBS (short bowel syndrome) to enhance their intestinal adaptation and nitrogen balance, and thereby the potential to allow for the weaning of TPN (total parenteral nutrition) and for an increase in oral intake.
  - The RDA (Recommended Daily Allowance) used to be the terminology standard for some nutrient supplements, but the term DV (daily value) is now preferred.

- Deficiency of vitamin D worsens any associated deficiency of calcium
  - If the patient has a low serum calcium concentration secondary to malabsorption, check their vitamin D concentration and if low, supplement the oral intake of calcium with calcifediol (25-hydroxy vitamin D).
  - Correction of hypocalcemia is difficult unless any associated serum magnesium
  - Deficiency is also corrected.

SO YOU WANT TO BE A GASTROENTEROLOGIST!

A patient with an extensive small bowel resection has hyocalcemia and elevated PTH concentration, normal serum vitamin D and magnesium concentrations. Oral supplement of calcium fail to correct nutritional therapy.

- Give the serum biochemical measurement which may help to make the diagnosis and lead to the correct nutritional therapy.
  - The presence of hypokalemia would raise the possibility of depletion of magnesium from the cells despite the maintenance of a normal serum magnesium concentration.
  - Correction of the intracellular magnesium concentration would allow for the expected release of PTH into the serum, its action on end organ tissue, and correction of the refractory hypocalemia.
  - And don't forget to correct any persisting hypokalemia.

"Enjoy the moment. You get too soon old and too late smart."

Grandad

SO YOU WANT TO BE A GASTROENTEROLOGIST!

Dietary fat intake, except for MCT (medium-chain triglyceride-based oil or liquid supplement), is often restricted in persons with steatorrhea, such as from the short bowel syndrome (SBS).

- Give the circumstance when dietary intake of long chain fatty acids may be increased in persons with steatorrhea, and explain the rationale.
    - Increasing oral fat intake may worsen the patient's diarrhea and steatorrhea.
    - Fat has a high energy density, and some patients with a short bowel syndrome who are losing weight may be willing to tolerate additional diarrhea while gaining weight as the result of increased intake of fats.

Additional calorie intake can be achieved with the intake of beverages containing both fructose and glucose.

FRUCTOSE-ASSOCIATED DIARRHEA

- Give the explanation why the amount of ingested monosaccharide fructose is not simply increased, rather than adding glucose to the fructose.
    - Glucose, galactose, sucrose (a disaccharide comprised of glucose plus fructose), and some amino acids actually increase the absorption of fructose.
    - Adding more fructose would result in only a modest increase in fructose absorption and therefore energy intake, whereas adding glucose provides calories from the glucose, as well as additional calories from the enhanced and more efficient absorption of fructose.
    - 10% of normal persons malabsorb some of a 25 g dose of fructose, and 80% of persons malabsorb some of a 50 g dose of fructose; by adding glucose to a beverage containing fructose, fewer adverse symptoms will develop from fructose malabsorption (but think of all super calories).

A patient is suspected to have GI symptoms from fructose malabsorption. The person does not wish to completely eliminate their intake of fruit, beverages sweetened with high fructose corn syrup or honey. Because of

their “sweet tooth”, their reduced intake of fructose is supplemented with sorbitol-containing candies. Their diarrhea, bloating and flatus worsen.

- Give an explanation why sorbitol-containing products should not be given to persons with fructose intolerance.
    - Sorbitol reduces the absorption of fructose, thereby increasing its concentration in the bowel lumen, increasing the osmolality in the lumen, thereby worsening the symptoms from the malabsorption of this monosaccharide.

- Give the formulation of pancreatic replacement, enzymes which are most efficacious in persons with hypochlohydria, or delayed gastric emptying.
    - Preparations of pancreatic replacement enzymes are microencapsulated to protect the enzymes from acid-sensitive proteolytic digestion in the duodenum.
    - If the luminal concentration of acid is low, or if there is dysregulation of gastric emptying; then the use of non-encapsulated enzymes may be recommended.

SO YOU WANT TO BE A GASTROENTEROLOGIST!

A patient with severe UC has a proctocolectomy with temporary ileostomy. The patient has mild distal leg pyoderma gangrenosa (PG), responding to local therapy including topical tacrolimus.

- When the patient develops ileostomy dysfunction and you examine the stoma, what are you specifically looking for with regards to the stoma?
    - Pyoderma gangrenosa (PG) may involve the stoma after a patient with UC has a proctocolectomy.
    - The PG is treated in the usual manner with local therapy (which may be possible given its location) as well as with the extensive list of systemic options, noted above.

SO YOU WANT TO BE A GASTROENTEROLOGIST!

Weight loss after RYGB may be partially from the restriction of food intake, and partially from the associated malabsorption.

- Give the **changes in GI peptides** which occur after RYGB and which may contribute to the improved insulin secretion, glucose tolerance, and weight loss.
  - Malabsorption in the jejunum leads to ↑ delivery of nutrients to the ileum
  - ↑ nutrients in the ileum lead to
    - ↑ PYY (peptide YY)
    - ↑ GLP-1 (glucagon-like petide-1)
    - ↑ GIP (glucose dependent insulin otropic polypeptide)

With rapid weight loss after bariatric surgery, a woman's menses may stop. In any situation when menses stop, you would suspect pregnancy and you would arrange pregnancy testing.

- Give the reason why this index of suspicion should be high in the post-bariatric surgery female patient.
  - Fertility improves with the post-surgical weight loss

SMALL BOWEL TUMORS

Small Bowel Stromal (Mesenchymal) Tumors (GISTs)

- Types
  - GIST (gastrointestinal stromal tumors)
    - Usually in stomach or small intestine
  - Site
    - Stomach ~70%
    - Small bowel ~25%
      - GIST comprises in ~85% of stromal tumors in the small intestine.
    - Colon / rectum 5%
  - Malignant potential
    - All GISTs > 10 m

- Genetic mutations
  - Mutational activation of genes
    - KIT
    - PDGFRA
    - DC117

- Marker for GIST
  - C-kit (a stem cell factor receptor) (~99%)
    - CD34 (a hematopoietic cell progenitor cell antigen) (70%)
    - Smooth muscle actin (20% to 30%)
    - S 100 protein (marker of neural differentiation)
  - Miscellaneous
    - Fat
      - Lipoma
      - Liposarcoma
    - Muscle
      - Leiomyomas
      - Leimyosarcomas
    - Nerve
      - Schwannomas

"The difference between how a person treats the powerless versus the powerful is as good a measure of human character as I know."

Robert Sutton

- Desmoid tumors
- Endo- or exogastric (into or away from lumen, respectively)
- Exogastric dislace rather than invade adjacent tissue
- GIST and leiomyomas may be both endo- and exogastric, giving a dumbbell shape
- GIT and leimyosarcomas
  - Usually exogastric
- Leiomyomas are multiple in ~25%

- Diagnosis
  - EUS plus FNA
  - Medical treatment
    - TK (tyrosine kinase) inhibitors, e.g. imatimib, used as adjuvant or no adjuvant therapy (before surgical resection)

- Surgical treatment
  - Segmental resection for ≥ 2 cm; leaving the tumor pseudocapsule intact
  - Obtain negative tumor resection margins
  - Laparoscopic resection is possible
  - Neoadjuvant therapy with imatinib
    - GISTs ≥ 3 cm
      - ↓ GIST recurrence is post-op year 1
  - Duodenal GIST
    - Duodenectomy if possible (no involvement of papilla of Vater)
      - Pancreaticoduodenectomy (with involvement of papilla)
      - Neoadjuvant therapy with imatinib (a TKI) may be beneficial for duodenal GIST
  - Jejunum / ileal GIST
    - Enblock segmental resection with TFM (tumor-free margins)
    - Do not resect regional lymph nodes

COLON

IRRITABLE BOWEL SYNDROME (IBS)

- Diagnosis of IBS remains solid
  - < 10% have an altered diagnosis

➢ Therapy
- High placebo response rates (~25%) seen in therapeutic trials
- Important for there to be a strong patient-physician relationship (not all GIs enjoy looking for IBS patients, or are particularly good at it)
- Remember to determine the patient`s most prominent symptom, e.g.
  - Diarrhea (IBS-D)
  - Constipation (IBS-C)
  - Diarrhea attenuating with constipation (IBS-D/C, or IBS-A)
  - Pain
  - Bloating
- Patient education
  - Validation
  - Empowerment
- Diet individualize exclusions after establishing cause-and-elimination benefit with the following
  - Lactose
  - Fructose
  - Sorbitol
  - "gassy" foods (note that many of these are FODMAPs [see below])
    - Apricots
    - Bananas
    - Beans
    - Broccoli
    - Brussel's sprouts
    - Cabbage
    - Carrots
    - Onions
    - Prunes
    - Wheat germs
  - Gluten (gluten sensitivity, without celiac disease diagnosed)

- "**FODMAPs**" (fermentable oligo-, di- and monosaccharides and polyols)
  - Fructans (in wheat, onions, artichokes)
  - Fructose (in legumes, cabbage, Brussel's sprouts)
  - Galactose
  - Lactose
  - Mannitol
  - Sorbitol
  - Xylitol
- Fiber is of no proven benefit, except possibly in constipation-predominant IBS (IBS-C)
- Do not exceed 30 gm per day of fiber, even if the constipation responds (30 g is the peak level of benefit before ↑ AEs)

- Physical activity
  - ↑ general well-being and general health
  - Moderate-to-vigorous physical activity, 20 min to 60 min, 3 to 5 days per week for 12 weeks

Clinical	↑ activity	Low level activity
Improved	43%	26% (p = 0.007)
Worsening	8%	23% (p < 0.01)

- Psychosocial therapy
  - Cognitive behavioral therapy
  - Psychotherapy
  - Hypnosis
  - Acupuncture
  - Biofeedback
  - High variable methodologies, and results
  - Meta-analysis suggests RR of IBS symptoms persisting with psychotherapy to be 0.67

- Medications
  - Adjunct therapy for predominant bowel compliant of diarrhea or constipation, including lubiprostone 8 µg po bid, for up to a year
  - Pain control
  - The Menu of medications
    - 5HT4 agonist
    - Amitryptyline
    - Anticholinergics
    - Bulking agents – psyllium, methylcellulose, fiber
    - CFTR stimulants
    - Chloride- channel agonists
    - Cholinergics: neostigmine, bethanechol
    - Colchicine
    - Desipramine
    - Doxepin
    - Lubricant – mineral oil
    - Motilin agonist
    - Osmotic laxatives – M of M, lactulose, PEG, sorbitol, mannitol
    - Peppermint oil
    - Prokinetics – dopamine
    - Prostaglandins
    - Stimulant laxatives – Senna, Bisacodyl, castor oil
    - TCAs, SSRIs
    - Trimipramine

Abbreviation: IBC-C, constipation-predominant IBS

Adapted from: Connor BA. *Clin Infect Dis* 2005;41 suppl 8:S577-86.; and Spiller RC. *Gastroenterology* 2003;124(6):1662-1671.

"The decisions of our present are the architects of our future."

Dan Brown

- Note: relatively small therapeutic gain (TG) between active agent (AA) and placebo (PL)

AA	PL	TG
53%	41%	12%

  - Improving bowel habit
  - Anti-depressants
    - Low dose (below dose used to treat depression)
      - TCAs (tricyclic anti-depressants)
      - SSRIs (selective serotonin reuptake inhibitors)
      - SNRIs (serotonin norepinephrine reuptake inhibitors)

      RR 0.66 NNT 4

- Note
  - Proven benefit in children
  - Onset of benefit ~ 4 wks
  - May worsen constipation because of anti-cholinergic effect
  - Anti-anxiolytics (benzodiazepines)
    - Short-term (< 2 weeks) only for acute situational anxiety
    - ↑ pain (↓ pain threshold, ↑ GABA (gamma aminobutyric acid) receptors
    - ↑ habituation, rebound withdrawal, drug interactions
  - 5-HT (hydroxytryptamine [serotonin] ¾ receptor antagonists / agonists (signaling agents)
    - 5-HT3 receptor antagonists
      - Small benefit (TG) for diarrhea, pain, global improvement
      - Restricted release because of concern re development of ischemic colitis
  - Antibiotics in IBS patients with proven small intestinal bacterial overgrowth (SIBO)
  - Peppermint oil
    - 187 mg to 225 mg po bid to tid to qid before meals
    - TG in pain response, 18% to 46%
  - CAMs (complimentary alternative medicine)
    - Pre/probiotics
    - Herbal medicine
    - Acupuncture

    } Patients may believe these are effective; not evidence-based

The MCQ stem may suggest IBS, but IBS symptoms may macquerade in several treatable conditions

- Give 5 treatable conditions, which may mimic IBS.
  - Celiac disease
  - Lactose intolerance
  - Gluten intolerance (different from celiac disease)
  - SIBO (small intestinal bacterial overgrowth)
  - Cholerrheic diarrhea (bile salt wastage)
  - Microscopic colitis (collagenous colitis and lymphocystic colitis)

- **Education and Support**
  - IBS tends to be a life-long disorder
  - A good physician-patient relationship has been associated with reduced use of medical services
  - Listen to the patient
    - Why now?
    - Are there any particular concerns?
    - What are the expectations of the encounter?
  - Reassure the patient. validate their concerns
  - Become an effective communicator
  - Physicians effectively facilitate the doctor-patient relationship and the dynamic exchanges that occur before, during, and after the medical encounter.

  - Key competencies:
    - Develop rapport, trust, and ethical therapeutic relationships with patients and their families
    - Accurately elicit, synthesize and convey relevant information and perspectives of patients and families, colleagues
    - Develop a common understanding on issues, problems and plans with patients and families, colleagues and other professionals to develop a shared plan of care
    - Convey effective oral and written information about a medical encounter.

- Education regarding the pathophysiology of the disease, and reassuring anxious patients who may have been symptomatic longterm without a diagnosis
- Keep clear documentation of discussions, clinical reasoning in chart and letters to other involved physicians

- **Caveats to a "Let's Try This For a While" Approach in IBS**
  - Variable definition of IBS
  - Definition of "response" to therapy
    - Global response vs. measurable endpoints
  - Spontaneous fluctuation in symptoms over time
  - High placebo response rate (~30%)

- **Diet**
  - Fiber (*RCT evidence*)
    - May benefit constipation and provide some global symptom benefit
    - Not helpful for pain or diarrhea
  - Exclude lactose intolerance
  - Reduce excess fructose, fatty foods, gas-producing foods, caffeine, alcohol
  - Reduce FODMAPs - fermentable oligo- di- and mono-saccharides and polyols
  - Exclusion diets
    - Can measure IgG antibodies to foods (not generally necessary or useful)
  - Probiotics
    - Variable findings for a wide spectrum tested

- Give 5 **classes of medications** to treat IBS
  - Anti-spasmodics and Anti-cholinergics
    - Anticholinergic vs. non-anticholinergic antispasmodics
    - Meta-analysis of 23 RCTs: antispasmodics superior to placebo, but study is of questionable quality
    - Anticholinergic anti-spasmodics do not have well-established efficacy
      - More useful for postprandial pain if taken 30 mins prior to eating
    - Non-anticholinergic antispasmodics (mebeverine – smooth muscle relaxant, selective CCB [pinaverium], opiate agonists [trimebutine]) may have modest benefit for pain.

- Antidiarrheals
  - Loperamide efficacious in RCTs for IBS with diarrhea
    - Does not improve abdominal pain or bloating
    - Best if taken regularly/prophylactically
    - Doses range from 2-16 mg/day
  - Bile salt-sequestering agents and bismuth subsalicylate supported anecdotally
- Serotonin (5-HT) Signaling Agents
  - 5-HT is a key neurotransmitter in the gut
    - Enteroendocrine cells release 5-HT into the submucosa in response to luminal conditions and state of mucosa
    - Submucosal nerves have receptors for 5-HT which mediate pain and initiate peristaltic reflex
    - Some enteric interneurons also use 5-HT for signaling
  - Alterations in 5-HT release or sensitivity of neurons to serotonin are postulated in IBS
  - Modulation of 5-HT3 and 5-HT4 receptors is effective in treatment in some patients with IBS
- Serotonin Receptor Drugs
  - Tegaserod, serotonin type 4 receptor agonist (5-HT_4)
    - Efficacy in constipation-predominant IBS
    - Release of acetylcholine and, prokinetic effects
    - Withdrawn in US/Canada – increased CVS, cerebrovascular events
  - Alosetron, 5-HT_3 antagonist
    - Indicated for diarrhea-predominant IBS
    - RCT evidence for “adequate” relief of IBS pain after 3 months: 60% (alosetron) vs. 41% (placebo)
    - Meta-analysis (3 studies) showed 1.6 RR for global improvement
    - Restricted use – concern for ischemic colitis, severe constipation

- Pain
  - Presence for at least 3 months, with onset of at least 6 months before diagnosis of:
    - Continuous or nearly continuous abdominal pain; and
    - No or only occasional relationship of pain with physiologic events (e.g. eating, defecation, or menses); and
    - Some loss of daily functioning; and
    - The pain is not feigned (e.g. malingering); and
    - Insufficient symptoms to meet criteria for another disorder of gastrointestinal function that would explain the pain

- Give 5 categories/classes of drugs used for pain in functional GI disorders.

Category	Examples/typical doses	Comments
○ Opiate analgesics	Hydrocodone 5-10mg QID	Avoid if possible ; chronic use should be monitored by pain management physician
○ Central opiate agonists	Tramadol 50mg TID-QID	May cause GI side effects: nausea, vomiting, constipation
○ NSAIDS	Ibuprofen 400mg QID	Beware dyspepsia, ulcer not significant
○ Tricyclics SSRI/SNRI	Paroxetine 20mg daily Duloxetine 30-60mg daily	Good choices if coexisting panic disorder or depression
○ Anticonvulsants	Gabapentin 300mg TID	Sleepiness a problem with higher doses
	Pregabalin 50-100mg TID	

Printed with permission: Schiller LR. *2008 ACG What's new in GI pharmacology course book*: pg. 34.

Note that some of these agents used to treat abdominal pain in IBS may worsen constipation

- Hypnotheapy
  - Gut-directed hypnotherapy done in highly specialized research centers is an effective treatment alternative for patients with refractory irritable bowel syndrome (IBS), but the effectiveness is lower when the therapy is given outside.
  - The effectiveness of gut-directed hypnotherapy is superior to the available pharmacological treatment options for IBS.
- Cognitive behavior therapy may prove to be helpful

Please also see: Thompson WG. Chapter 64. In: Therapeutic Choices. Grey J, Ed. 6th Edition, Canadian Pharmacists Association: Ottawa, ON, 2011, Table 4: Drugs used for the Management of Irritable Bowel Syndrome, page 864.

- Diarrhea
  - Anti-laxatives
  - Bile salt binders
  - Peptobismal

- Give a summary of drugs commonly used for irritable bowel syndrome as well as for diarrhea during pregnancy.

Drug	FDA Pregnancy use category	Usual dosage	Additional comments
○ Tegaserod	B	6 mg twice daily	Limited data; should be considered only when other measures fail to control constipation – predominant irritable bowel syndrome
○ Loperamide	B	2-4 mg daily or after each unformed stool	Antidiarrheal agent of choice during pregnancy
○ Diphenoxylate with atropine sulphate	C	1-2 tablets four times daily	Should be avoided during pregnancy. Contains 2.5 mg diphenoxylate plus 0.025 mg atropine per tablet
○ Dicycloverine (dicyclomine)	B	10-20 mg four times daily	Should be reserved for women with refractory symptoms
○ Hyoscyamine	C	0.125-0.250 mg every 6 h as needed	Should be reserved for women with refractory symptoms
○ Tricyclic antidepressants	C/ D	Dose differs according to retail brand	**Questionable safety** in pregnancy; use should be limited to the severely symptomatic

Printed with permission: Thukral, Chandrashekhar., and Wolf, Jacqueline L. *Nat Clin Pract Gastroenterol Hepatol* 2006; 3(5): pg. 261.

- Antidepressants
  - TCAs
    - Meta-analyses have included low-quality studies, report NNT 3-4 for improvement in global well-being
    - Large RCT - Desipramine vs. placebo – in female patients 60% vs. 47% response
    - May be most beneficial in diarrhea-predominant IBS
    - Up to 40% discontinue use because of intolerance
    - Questionable safety in pregnancy
  - SSRIs
    - Fewer side effects, RCTs report more mixed results

- Antibiotics
  - Largest and most rigorously designed studies for IBS are with rifaximin
  - Two Phase 3 RCTs (1260 pts) for non-constipation IBS: rifaximin 550mg tid x 14d improved global and individual symptoms (bloating, AP, stool consistency) vs. placebo
    - Benefits persisted up to 3 months
    - Side effects: Safe – no C difficile
    - Prognosis (> 10 weeks unknown

- Constipation-treating medications (please see next page)

"The whole purpose of education is to turn mirrors into windows."

Sydney J. Harris

CONSTIPATION

- Laxatives

Drugs used to treat constipation

Remember "BOLSSS μ"

B Bulk-forming fiber preparations

- Psyllium hydrophilic muciloid polycarbophil calcium, sterculia gum
- The maximum benefit of fiber is reached at 30 g / day.

O Osmotic agents

- Lactulose 15 mL – 30 mL od bid po
- Milk of magnesium sulfate, polyethylene glycol 3350, sodium phosphates, fleet enema
- Glycerine suppositories 2.6 g po → bid → prn pr

L Lubricants

- Glycerin
- Mineral oil po (Agarol® 100 mL – 20 mL qhs po bid
- Fleet enema mineral oil od prn
- Lavage: PegLyte, Colyte
- To avoid early adverse effects and to avoid loss of patient compliance, increase the dose of fiber slowly (to maximum tolerable dose, but < 30 g /day).
- Avoid the use of castor oil in pregnancy, to reduce the risk of premature uterine contractions.

S Softener

- Docusate calcium 240 mg od bid po
- Docusate sodium (Colace ®) 100 mg od bid po

Stimulants

- Stimulant laxatives are more effective than fiber.
- Dulcolax po 5 mg – 10 mg po prn, pr suppository 10 mg po prn
- Senna 16.2 mg – 32.4 mg (2-4 tabs), max 8 /day

Secretion of chloride

- Fiber
- Osmotic agents
- Stimulants
- Prokinetics
- Chloride channel activatiors (modulators)

μ Opioid receptor antagonist

- Methynaltrexone
  - Light weight (38 kg - < 62 kg) 8 mg every 2 days SC
  - Heavy weight (62 kg - < 114 kg) 12 mg every 2 days SC

Adapted from: Maclean C. Chapter 56. In: Therapeutic Choices. Grey J, Ed. 6th Edition, Canadian Pharmacists Association: Ottawa, ON, 2011, page 735-746.

- Note
  - No RCTs of laxatives efficacy in IBS
  - PEG likely better tolerated than osmotic laxatives
  - Stimulant laxatives can also induce abdominal cramping and pain (generally unsatisfactory for patients with IBS)

- **Modulation of Chloride Secretion**
  - Chloride secretion by intestinal mucosa is main mechanism of fluid secretion in intestine
  - Mediated by chloride channels in apical membrane of enterocytes that permit chloride from interior of cell to lumen
    - CFTR
    - Chloride C-2 channel
  - Na^+ and water follow to maintain electrical and osmotic equilibrium
  - No evidence that chloride secretion is defective in constipation-predominant IBS
  - Lubiprostone
    - Prostaglandin derivative, activates chloride C-2 channels and promotes secretion
    - Approved for treatment of IBS-C in US
    - Global response rates 18% (lubiprostone) vs. 10% placebo
    - Significantly more likely than placebo to improve individual symptoms, e.g., stool consistency, straining, constipation, QOL
    - ACG IBS Task Force – 8mcg bid more effective than placebo in relieving global IBS Sx in women
    - S/E – Nx (8%), diarrhea (6%)

- Linaclotide
  - Guanylate cyclase-C receptor agonist, stimulates production of cGMP, which activates CFTR
  - Two Phase 3 RCTs (>1600 pts) found licaclotide superior to placebo for overall and individual Sx of IBS-C
  - S/E: Diarrhea

- Complementary Alternative Medicine (CAM)
  - 11-53% of IBS patients in N. American and Europe have used at least one type of CAM technique
  - Prebiotics
    - Non-digestible food ingredients that beneficially affect the host by selectively stimulating the growth/activity of health-promoting bacteria in the colon
    - Few studies
  - Acupuncture
    - May alter visceral sensation and motility by stimulating somatic nervous system and vagus nerve
    - 2006 Cochrane review of 6 RCTs: most of poor quality, inconclusive evidence
    - Subsequent large study showed superiority of acupuncture and sham acupuncture over no treatment
  - Herbal medicines
    - Peppermint oil is a cross between winter mint and spearmint, active principle being menthol
    - 1998 meta-analysis of 5 RCTs showed significant global improvement of IBS-Sx compared with placebo
    - Recent RCT in Taiwan (110 patients), peppermint oil vs. placebo x 1 month – patients in treatment arm had less abdominal distention, stool frequency, flatulence

BLOATING, DISTENTION, EXCESS GAS

- The patient
  - Feels - Bloated
  - Sees - Distention
  - Passes - Perceived excessive flatus ("gas")
  - May occur with or without IBS

- Belching
  - Mechanisms
    - ↑ intake
      - Aerophagia
      - "gassy" foods
      - Chewing gum
      - Carbonated beverages
    - ↓output
      - Gastroparesis
    - ↑LES relaxation
      - Chocolate
      - Mints
      - Fatty acids
    - ↑ production
      - ↑ bacterial overgrowth and breakdown of carbohydrates (CHO)

- Flatulence
  - Normal
    - 10 to 20 times per day
    - 500 to 1500 mL per day
  - Mechanisms
    - ↑ production
      - SIBO
      - Maldigestion of CHO
    - ↓ motility
    - ↑ sensitivity (intestinal hyperalgesia)

CHRONIC IDEOPATHIC CONSTIPATION (CIC)

- Remember
  - IBS, constipation
    - Predominent requires a component of abdominal pain; CIC does not have pain component

- Treatment
  - May be different for the three major types of constipation:
    - Normal transit
    - Slow transit (inertia)
    - Functional defecation disorder
      - Suppositories / enemas
      - Botulinum toxin injection into the puborectalis muscle
      - Relaxation exercises

  - Life style changes
    - Diet
      - Fiber up to 30 gm per day
      - Sorbitol / fructose
    - Exercise
    - Fluids

  - Laxatives
    - Bulk-forming laxatives
      - Psyllium
      - Methylcellulose
      - Polycarbophil
    - Osmotic agents
      - PEG (polyethylene glycol) electrolyte solution, e.g. GOLITELY® 34 gm in 480 mL water, take up to 34 gm per day, or
      - 17 gm GOLITELY® in 240 mL, plus a stimulant (e.g. bisacodyl [Dulcolax®], senna [Senokot®]), or misoprostol
      - Sorbitol, lactulose (20 gm [30 mL] qid
    - Stimulant laxatives
      - Please see above

- Warm water enemas 100 to 200 mL per day
- Sodium phosphate enemas (use with much caution in older persons)
- Lubricant glycerine suppositories
- Lubisterone (Cl- channel agonist), 8 µg po bid for 2 weeks
- Misoprostol 20 µg po q 2 days, then at weekly intervals increase dose by misoprostol 200 mg po q 2 days)
- Colchicine 1 mg po per day, or 0.6 mg pot id
- Linaclotide (guanylate cyclase-0 receptor agonist)
- Procalopride
  - $5HT_4$ prokinetic
  - 1 mg to 4 mg per day

- Behavioral training
  - Biofeedback
    - Pelvic muscle dyssynergy (dyssynergic defecation)
    - Dyssynergic defecation is associated with slow transit constipation
    - Biofeedback also works when dyssynergic defecation is associated with slow transit constipation (but s not effective for slow transit constipation without associated dyssynergy)

- Surgery
  - Repair
    - Rectocele
    - Prolapse
    - Intussusceptions
  - Subtotal colectomy with ileorectal anatonosis
    - Subtotal colectomy with ileorectal anastomosis may appear to be an extreme treatment for a benign disorder, but chronic constipation may be severe, disabling, and completely eliminate any semblance of patient quality of life. However, in properly selected surgical candidates, ~ 90% of patients are satisfied with the results.

- Selection criteria
  - Chronic, severe, disabling symptoms
  - Slow colonic transit
  - No pelvic flow dysfunction
  - No pseudo-obstruction
  - No abdominal pain

- Give the FDA category of laxatives in pregnancy.

Safe (B)	Caution (C)	**Unsafe** (D)
- Lactulose - Glycerine - Polyethylene glycol (PEG) - Bulking agents - Bisacodyl	Saline osmotic laxatives Castor oil Senna Docusate sodium	**-Anthraquinones** **-5HT4 agonists** **-Prostaglandins (misoprostol)**

Adapted from: Cullen G, and O'Donoghue D. *Best Pract Res Clin Gastroenterol* 2007; 21(5): pg. 815.; and Thukral C, and Wolf JL. *Nat Clin Pract Gastroenterol Hepatol* 2006; 3(5): pg. 260.; Printed with permission: Kane SV. *AGA Institute 2007 Spring Postgraduate Course Syllabus:*511.

"The darkest places in hell are reserved for those who maintain their neutrality in times of moral crisis."

Dante Alighieri

FECAL INCONTINENCE

- Give medical and surgical treatments of fecal incontinence.
  - Treat underlying cause (s)
  - Supportive therapy (the patient)
    - Education/counseling/habit training
    - Trained defecation
    - Diet (fiber; lactose, fructose, reduce caffeine intake)
    - Incontinence pad
    - Perianal hygiene/skin care
  - Pharmacological (the stool)
    - Fiber
    - Loperamide
    - Lomotil
    - Codeine
    - Cholestyramine/colestipol
    - Estrogen
    - Phenylephrine
    - Sodium valproate
  - Biofeedback therapy
    - Anal sphincter muscle strengthening
    - Rectal sensory conditioning
    - Recto-anal coordination training
  - Perianal
    - Anal plugs
    - Pessary
    - Kegal exercises
    - Sphincter bulking (collagen, silicone)
    - Anal electrical stimulation
    - Injection sclerotherapy
    - Sacral nerve stimulation

- Surgery
  - Artificial anal sphincter
  - Sphincteroplasty
  - Anterior repair (rectocele)
  - Gracilis/gluteus muscle transposition +/- stimulation
  - Colostomy
  - Pelvic reconstruction
  - Options: rubber band ligation
  - Surgical excision
  - PPH-Stapled Hemorrhoidopexy

Adapted from: Schiller L. *Sleisenger & Fordtran's gastrointestinal and liver disease: Pathophysiology/Diagnosis/Management* 2006: pg. 207.

- Treatment of perianal disease
  - Habits
  - Obsession with cleaning
  - Cleaning
  - Sitz bath
  - Steroid cream
  - Anusol with lidocaine or HC
  - Paper
    - Perfume
    - Colouring
  - No soap near perineum
  - Hot water may make itch worse (histamine release)
  - Diet
    - Caffeine r/o
    - Spices
    - Beer is bad
  - Gloves, cut nails
  - Stretch
    - ↓ spasm

- CCBs (calcium channel blockers), diltiazem 2% qid x 28 days, Anusol HC / Anusol with lidocaine
- GTN 0.2% paste / ointment
- Breaks the viscous cycle
- Botox injection
  - Normal saline dental line, 4 quad using scople or use anoscope
- Lord procedure
  - Manual dilation in or under anesthesia (risk of incontinence)
- Lateral sphincterotomy (at 3 to 5 o'clock, to relax sphincter)
- Fissurectomy
- Tags "extra skin" like a callus on top of your hemorrhoid": hypertrophic squamous epithelium

"Education is learning what you didn't know you didn't know."

George Boas

"Absence of evidence is not

Evidence of absence"

Anonymous

ULCERATIVE COLITIS (UC)

- Give the **indications** for the use of infliximab in persons with ulcerative colitis.
  - Induction of remission in adults and children who are outpatients with moderately to severely active disease who have failed therapy with and are treated concomitantly with aminosalicylates, corticosteroids, or immunomodulators
  - Maintenance of remission after infliximab for induction therapy
  - Hospitalized patients with severe UC
  - Steroid-sparing
  - Extraintestinal manifestations of UC
    - Spondyloarthropathy
    - Pyoderma gangrenosum
    - Unresponsive iritis/uveitis

Adapted from: Sandborn W. *AGA Institute PostGraduate Course book* 2007;138.

- **Long-term treatment goals** of IBD patients
  - Rapidly relieve symptoms
  - Avoid surgery
  - Avoid hospitalization
  - Improve QoL
  - Heal mucosa

Source: VanAssche G et al. page 139. Insights Into Patient and Physician Communication and Expectations: Results of a Large Pan-European Survey of Physicians and Their Patients With Inflammatory Bowel Disease. ECCO 2008.

Wisdom is the reward you get for a lifetime of listening

when you'd have preferred to talk.

Doug Larson

	Drug	Induction of remission	Prevention of relapse
○	5-ASA topical	Versus oral 5-ASA	Versus placebo
		RR of no remission with topical 5-ASA = 0.82; 95% CI 0.52 – 1.28	RR = 0.60; 95% CI 0.49 – 0.73 (Ford et al., Am J Gastroenterol 2012; 10: 513-519)
		Combined vs. oral RR = 0.48; 95% CI 0.65 Ford et al., Am J Gastroenterol 2012; 107: 167-176.	RR of relapse = 0.65; 95% CI 0.55 – 0.76 (Ford et al., Am J Gastroenterol 2011; 106: 601-16) RR = 0.64; 95% CI 0.43 – 0.95 combined vs. oral RR of relapse = 0.48, 95% CI 0.17 – 1.38

Overview

- **5-ASAs** are effective at inducing remission in mild-to-moderately-active UC RR of no remission with 5-ASAs of 0.79; 95% CI = 0.73 – 0.85; NNT = 6, and are effective at preventing relapse in quiescent UC.
  - doses of 5-ASA ≥ 2.0g/day are more effective than < 2.0g/day for remission (RR = 0.91; 95% CI = 0.85 – 0.98), but doses > 2.5g/day do not provide higher remission rates and may be associated with a higher risk for adverse events.
- **Corticosteroids** are effective at inducing remission in active UC (Relative risk [RR] of no remission, 0.65; 95% CI = 0.45 – 0.93), and are not recommended at preventing relapse in quiescent UC.
- **Azathioprine/6-MP and methotrexate** are not recommended for inducing remission in active UC (only trend for benefit, RR = 0.85; 95% CI = 0.71 – 1.01); whereas azathioprine/6-mp (but not methotrexate) are possibly effective at preventing relapse in quiescent UC (RR = 0.60; 95% CI = 0.37 – 0.95).
- **Cyclosporin IV** is effective in improving symptoms and reducing immediate colectomy rates in persons with severely active UC not responding to corticosteroids.

- **Antibiotics** have shown a statistically sufficient effect at inducing remission in UC (RR of UC not in remission = 0.64; 95% CI = 0.43 – 0.96), but various antibodies have been studied and no one class can be recommended.

- **Infliximab** is effective at inducing remission in ambulatory patients with moderately-to-severely-active UC (RR = 0.72; 95% CI = 0.57 – 0.91), and at improving symptoms and halving the need for colectomy in hospitalized patients with severely active UC.
  - "Patients with UC refractory to conventional therapy which has responded to infliximab should best be considered for continuing therapy, since scheduled re-treatment is effective for maintaining response and reducing the risk of colectomy."
  - "Patients with early luminal CD have a higher chance of response to Anti-TNF therapy than those with longstanding disease."
  - "Patients with a high CRP have a higher chance of achieving and maintaining response to biological therapy than patients with a low or normal CRP."
  - "High trough concentrations of IFX have been associated with more durable maintenance of clinical response and low trough concentrations with potential loss of response."

- **Natalizumab** (anti – 24 integrin antibody) has not yet been adequately studied in UC to make a comment about the use.

Overview of Effect of Usual Therapies for Crohn disease (CD)[1,2] and for Ulcerative Colitis (UC)[2]Crohn disease (CD)

Drug	Induction of remission	Prevention of relapse
Standard GCS (glucocorticosteroids)	Versus placebo RR of no remission = 0.46, 95% CI 0.17-1.28	Do not use
Budesonide	Versus budesonide[2] RR = 0.82; 95% CI 0.68-0.98 Versus budesonide[2] RR = 0.73, 95% CI 0.63-0.98	Versus placebo RR= 0.93; 95% CI 0.83-1.04 Do not use

[1]This data is comprised from two studies, but because the heterogeneity, the overall effect was significant

[2]Glucocorticosteroids-related adverse effects were more common with use of standard GCS than with budesonide (RR = 1.64; 95% CI 1.34 – 2.00)

Ford et al., Am J Gastroenterol 2011; 106: 590-599.

○ AZA / 6-MP	RR of incidence remission = 0.87; 95% CI 0.71-1.06	Versus placebo RR= 0.64; 95% CI 0.34-1.23 Withdrawal triats RR = 0.39; 95% CI 0.21-0.74

Khan et al., Am J Gastroenterol 2011; 106: 630-642.

Drug	Induction of remission	Prevention of relapse
○ Antibiotics	Versus placebo RR = 0.85; 95% CI 0.73-0.99 Perianal CD RR = 0.8; 95% CI 0.66-0.98	Versus placebo RR= 0.62; 95% CI 0.46-0.84
○ 5-ASA topical	Versus oral 5-ASA RR of no remission with topical 5-ASA = 0.82; 95% CI 0.52 – 1.28 Combined vs. oral RR = 0.48; 95% CI 0.65 Ford et al., Am J Gastroenterol 2012; 107: 167-176.	Versus placebo RR = 0.60; 95% CI 0.49 – 0.73 (Ford et al., Am J Gastroenterol 2012; 10: 513-519) RR of relapse = 0.65; 95% CI 0.55 – 0.76 (Ford et al., Am J Gastroenterol 2011; 106: 601-16) RR = 0.64; 95% CI 0.43 – 0.95 combined vs. oral RR of relapse = 0.48, 95% CI 0.17 – 1.38

Khan et al., Am J Gastroenterol 2011; 106: 661-673.

Clinical Endpoint	Rate	Number needed to treat (NNT*; 95% CI)	
➢ Induction of Remission		**CD**	**UC**
o Aminosalicylates (5-ASA)			
– overall	32%	10-11	6
– high dose	43%	4	
o Steroids			
– prednisone/6 – methylprednisolone	60%	3	3
– budesonide 9 mg	51%	3-5	
o Antibiotics		11	7
o Metronidazole /ciprofloxacin, fistulizing disease		5	
o Thiopurines (> 12 weeks)			
– azathioprine/6-MP	56%	5	
o Methotrexate	39%	5	
o Cyclosporin		-	1.2
o Infliximab			
– Moderate	41%	3-8	
– Fistulising		3	
– Severe		6	
➢ Maintenance of Remission (prevent relapse)			
o aminosalicylates (5-ASA)	70%	13	4
o antibiotics		4	-
o azathioprine	66%	3-4	4
o methotrexate	65%	4	-
o infliximab	42%	5	-

[1]Adapted from: [2] Talley N.J. et al., Am J Gastroenterol 2011; 106: S2 – S25. Bebb JR and Scott BB, Aliment Pharmacol Ther 2004; 20: 151-159; and from
*NNT = 10 / RRR x BR (RRR, relative risk reduction; BR, baseline risk)

- Serological tests are seldom performed to distinguish between ulcerative colitis (UC) and Crohn disease (CD). Yet they frequently make an appearance on MCQs. Also smoking has a different effect in UC and CD, and this may be given as a clinical feature.

	UC	CD
– ASCA	Positive in 10%	Positive 60%
– p-ANCA	Positive in 75%	Positive in 10%
– Smoking	Helps UC	Worsens CD

"Buzzwords" which suggest the type of IBD (look for these words in the clinical scenarios of MCQs)

UC	CD
o Crypt abscess	– Granuloma
	– Perianal and disease
	– Rectal sparing
	– Skip lesions
	– Fistulae

ULCERATIVE PROCTITIS (UP)

- Inflammation of distal 15 cm of colon
- Present in 30% of UC patients at diagnosis
- Proximal spread to procosigmoiditis or distal UC (distal to splenic flexus); pancolitis, 50% in 10 years.

➢ Treatment

- Rectal (topical) therapy
  - 5-ASA suppositories (coat 10 cm of distal bowel)
    - 1 gm per rectum (pr) at bedtime each day for 4 weeks, then taper (q 2 days for 2 weeks, then q 3 days for 3 weeks)
    - Remission 93%
    - Maintenance 75% (after 1 attack, consider stopped remission therapy after 3 weeks, and wait to see what is the pattern of the patient's UP, i.e. frequent recurrences → maintenance Rx

- 5-ASA enemas (coat up to splenic flexure)
  - 4 gm pr at bedtime
  - Consider combining with 5-ASA po for greater effect

	Remission	
	5-ASA enemas	5-ASA enema plus 5-ASA po
4 weeks	34%	44%
8 weeks	43%	64%

- Steroid enemas / foams
  - Inferior to 5-ASA
  - Low systemic absorption, few AEs
  - Do not use longterm
- Budesonide enemas
  - Low systemic absorption
  - Use for failure of 5-ASA enemas
  - Do not use longterm

- Oral therapy
  - Use if patient cannot tolerate rectal therapy (suppositories, enemas)
  - Response po < pr
  - po steroids not used for maintenance (including budesonide)
  - Response usually seen in 4 weeks, then taper

➢ **Proctocolitis, left-sided colitis or pancolitis**, mild-to-moderate activity

- **5-ASA / mesalamine**
  - To achieve remission 5-ASA containing drugs, pr and po
  - Sulfasalazine 500 mg, tab II-III qid for 3 months
  - Asacol® 400 mg po, tabs II-III qid for 3 months
  - Mesalamine vs placebo, 0.79
  - Other 5-ASA 500 mg po tab II-III qid for 3 months (Salofalk, Mesasal, Pentasa, Lialda, Dipentum, Colazal, Apriso, etc)
  - Annual relapse on 5-ASA, 20%; not on 5-ASA, 80%
  - Trend for greater benefit of mesalamine vs sulfasalazine
  - Mucosal healing rates at 6 week 4.8 g / day, 80% 2.4 g / day, 68%
  - To maintain remission 50 mg po tab II bid
  - If patient foes not go into remission in 4 weeks, stop 5-ASA and start prednisone po

- Sample meta-analyses of efficacy of 5-ASA in UC (vs. placebo)

	OR
○ 5-ASA suppositories / enemas	
– Achieving remission distal colitis	7.4
– Maintaining remission	16.2
	RR
○ 5-ASA po	
– Achieving remission	0.79
– Maintaining remission	0.65
	OR
○ ↓ risk of CRC	0.51
○ ↑ risk of renal toxicity	2.48

Abbreviations: CRC, colorectal cancer; OR, odds ratio

- Is there a "better" 5-ASA product?

Product	Comparator	Outcome	Stats
○ Mesalamine	Sulfasalazine	Induction of remission	Trend
○ Balsalazine	Mesalamine	Induction of remission	RR 1.30

○ It is likely that all mesalamine preparations are similar effective

SO YOU WANT TO BE A GASTROENTEROLOGIST!

Unless you frequently check the US Food and Drug Administration (FDA) website, you may not have noticed that Asacol® and Asacol HD have had their pregnancy category changed from B and C. And MMX-coated mesalamine is not used in pregnancy.

- Give the reason for this change the FDA pregnancy category of Asacol®, give why MMX-5-ASA is not used in pregnancy.
  - It's all about the coating: the enteric coating of Asacol® was found to contain DBP (dibutyl phthalate), which when given in high doses to animal may cause abnormalities in skeletal formation and male reproductive system and the MMX coating is also contraindicated in pregnancy.

- **Glucocorticorsteroids (GCS)**
  - When disease activity continues after starting 5-ASA, or increasing from lower maintenance to higher active treatment dose
  - Never use for maintenance therapy
  - Prednisone 5 mg po tab 8 / day in am for 4 weeks, then with clinical important begin slow taper by eliminating one 5 mg tab each week (e.g. 40 mg for 4 weeks – 35 mg for 1 week, 30 mg or 1 week, 25 mg for 1 week ……. STOP)
  - Once taper of prednisone is nearing completion and patient is in remission, restart 5-ASA po.
  - If rectal complaints are prominent, may use co-therapy with steroid or 5-ASA enemas
  - If symptoms do not improve, stop improving or worsen after ~2 weeks of prednisone 40 mg po per day, then increase dose to maximum of 12 tabs (60 mg) per day.
  - If no response,
    - Do not continue increasing oral dose of prednisone
    - Begin IV steroids
    - Consider starting AZA (azathioprine) or po 6-MP
    - Consider anti-TNF biologics
  - If patient was already on 5-ASA when prednisone started, 5-ASA may be stopped.
  - To emphasize the learning point-do not use steroids in any form for maintenance therapy.

A patient with severe UC is hospitalized, placed on oral glucocorticosteroids (GCS), but does not respond.

- Give 5 molecular mechanisms of steroid resistance.
  - Abnormalities in absorption/metabolism (liver disease)
  - Altered number of GCS receptors, or altered numbers of isoforms (α, β, δ)
  - Altered affinity of GCS for GCS receptors
  - Reduced affinity of the GCS receptor ligands to bind to DNA
  - Altered expression of transcription factors (AP-1, NF-k B) and/or cytokines (IL-2, IL-4, p38 activated MAP kinase)
  - Genetic factors (primary steroid resistance, MDR-1 [P-glycoprotein 170], HLA class II allele DRB1*0103)

Adapted from: Farrell RJ, e al. *J Endocrinol* 2003; 178(3): 339-46.

- Give 5 clinical **causes of "steroid resistance**" in patients with "colitis" (factors causing persistence of symptoms).
  - Infection - C. difficile, CMV
  - NSAIDs
  - Smoking discontinuation
  - Drug interactions
  - UC with CD-like features – discontinuous disease, superficial fissuring ulcers, aphthous ulcers, ileal involvement, involvement of the upper GI tract, granulomas
  - CD with UC-like features – pancolitis, superficial colitis
  - Other forms of "colitis" that may mimic UC
  - Development of colorectal cancer (CRC)

- Give a clinical strategy for dealing with steroid resistance in patients with IBD, in whom the above factors causing persistence of symptoms have been excluded.
  - Adjust dose, change to IV
  - Higher dose of 5-ASA (controversial), or 5-ASA enemas
  - Cyclosporin
  - Azathioprine, 6-MP
  - Methotrexate
  - Biologics – anti TNF
  - Probiotics
  - Fish oil, nicotine patch
  - Colectomy

Adapted from: Mayer LF. *AGA Institute post graduate course book* 2007. pg. 109.

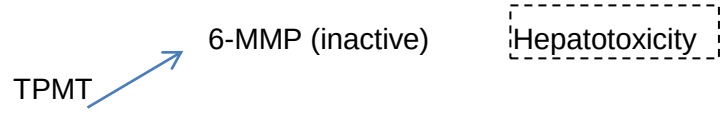
Pearls and Gems

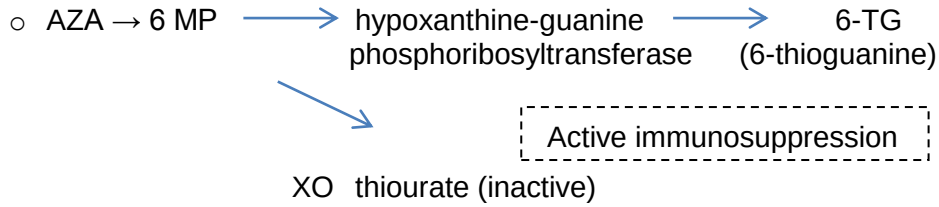
- When prednisone 40 mg to 60 mg po per day is not providing a satisfactory response, switch to methylprednisolone 40 mg to 60 mg IV per day.
- In the context of severe UC, the patients is considered to be steroids-refractory after 3 to 5 days of IV glucocorticosteroids, and "bridge therapy" with infliximab or cyclosporin plus azathioprine needs to be started, a colectomy depending upon the clinical scenario.
- If the UC patient is considered to be steroid-dependent, introduce immunosuppression, and if severe disease and cyclosporin fails or is contraindicated, consider colectomy

- **Immunosuppressants**
  - The immunosuppressants (azathioprine, 6-MP) and biologics (anti-TNF-α drugs) are generally considered in UC patients if they are steroid – refractory or steroid-dependent
  - Steroid-responsive disease: "meaningful clinical response to high dose glucocorticoids (prednisone 40 to 60 mg / day or equivalent) within 30 days for oral therapy or 7 to 10 days for IV therapy".
  - Steroid-refractory disease: "lack of meaningful clinical response to glucocorticoids up to doses of prednisone 40 to 60 mg / day (or equivalent within 30 days for oral therapy or 7 to 10 days [*] for IV therapy".
  - Steroid-dependent disease – "patients [initially] respond to glucocorticoids, but experience a dose of clinical response when glucocorticoids are tapered to less than 10 to 30 mg / day, or rapidly relapse once glucocorticosteroids are stopped".

From: Cohen RD and Stein AC, UpToDate April 2012.

- Azathioprine (AZA) and 6-MP in UC
  - Uses is for
    - Steroid non-response (seen in ~16% of UC patients)
    - Steroids-dependence: ≥ 4 months of continuous steroids to control symptoms (22%)
    - Frequent relapses (≥ 3 flares per year, despite 5-ASA





  - Mechanism of action
    - ↓ synthesis of purine, DNA, RNA
    - ↓ proliferation of T and B lymphocytes

↑ TPMT → ↓ 6-TG
↓ TPMT → ↑ 6-TG (↑ AEs from immunosuppression) low TPMT in 11% of people, negligible TPMP in 0.3%

- Dosage
  - AZA 2.5 mg/kg per day, continued indefinitely in UC patients who have achieved remission.
  - Dosage conversion of AZA to 6-MP ~50%
  - Allopurinol blocks xo; when ↓ XO; more 6-M is converted to 6-TG, so dose of 6-TG needs to be decreased.
  - Dose reduction or discontinuing AZA may be necessary if there develops bone marrow suppression (2%) or abnormal liver tests (0.5%).
  - Steroid-non-respondent, adding AZA ↑ likelihood of response ~50%
- If UC patient is steroid-dependent, adding AZA decreases steroid requirement by ~70%.
- Maintenance: AZA vs PL, RR of relapse – 0.4 to 0.6 absolute risk reduction of relapse -23%; NNT ~5
- 3 months for therapeutic effect to be achieved (cannot declare "non-response to AZA until after 3 mon use of full dose)
- AZA po = IV effectiveness

Action	WBC, x 10 (g)/L	Platelets, x 10(g)/L	ALT transaminases
– Reduction in dose	<4	<120	
– Stop AZA	<3	<80	> 50% of ULN (upper limit of normal) ↑ bilirubin (cholestasis)

Note: If jaundice develops while on AZA, the AZA should be stopped, and not restarted

- There is no therapeutic benefit for continuing 5-ASA to AZA when the AZA is used for 5-ASA failures
- Some patients may be continued on 5ASA while on AZA because 5-ASA → ↑ TG concentrations, and using the 5-ASA may allow the dose of AZA to be reduced.

SO YOU WANT TO BE AN IBDologist!

Patients who are hypersensitive to AZA, or cannot tolerate AZA for any reason, are able to tolerate 6-MP.

- Give the reason why 6-MP may sometimes be used by persons intolerant or hypersensitive to AZA.
    - When AZA is metabolized to 6-MP, the nitromidazole part of the AZA is lost.
    - The hypersensitivity reactionists AZA are partly to the nitromidazole moiety.
    - Only some intolerant persons who are switched from AZA to 6-MP are able to tolerate 6-MP, presumably because there are additional unknown reasons for intolerance besides nitromidazole.
- Give the generally accepted indications for performing a CT scan or MRI of the abdomen and pelvis in the patient with IBD (UC or Crohn disease).
    - Penetration
    - Abscess
    - Fistula
    - Perforation
    - Obstruction
    - Megacolon
    - Non-IBD conditions
        - Renal calculi
        - Cholecystitis
        - Diverticulitis

➢ **Severe / fulminant colitis**

- Severe
    - Stop 5-ASA used for previous maintenance therapy

"Don't worry about 'the neurobiological mechanisms of motivated learning' – just provide a safe, stimulating and welcoming environment."

Grandad

There are endoscopic scoring systems to determine the severity of UC, but risk stratification is based on the clinical assessment.

- Give the clinical factors upon which basis the patient is judged to have severe or fulminant UC.
    - Severe
        - > 6-8 BM per day
        - Bleeding
        - Fever
        - HR / PR > 90 bpm
        - ESR > 30 mm/h
        - Anemia
    - Fulminant
        - > 10 bloody BMs per day
        - Pain, fever, anemia, tachycardia

Clinical Alert

- In the patient with severe colitis, avoid doing barium enema (with or without contrast) or colonoscopy, for fear of causing megacolon, including toxic severe UC (because of transmural thickness of CD and the often associated fibrosis, megacolon is much less common in the patient with CD unless there is a fibrotic stricture or cancer).

- Make certain the patient has UC, not Crohn colitis, look at the subtle differences with CD
    - 5-ASA / sulfasalazine limited use for treating a relapse, or for maintaining remission
    - Immunosuppressants, including IM /SC methrotrexate, are used after 2 acute attacks requiring steroids
    - Cyclosporin is not effective for severe active disease
    - Biologics (anti-TNF therapy) is used for steroid plus immunosuppressant resistant disease, or for fistulising CD, or ascites

- Give the management of the patient with severe **ulcerative colitis** (Toronto Guidelines).

  - Admit to hospital
    - IV fluids and electrolytes
    - Review the diagnosis as UC, and not Crohn disease
    - Exclude enteric infections such as C. difficile, CMV, amebiasis (in appropriate geographical setting)
    - Caution patient that there is about 1 chance in 4 for the need to use cyclosporin, infliximab, or to consider colectomy

Severe UC – IV corticosteroids ~ ¾ respond

  - For the ¼ corticosteroid non-responders
    - Cyclosporin ~ ¾ respond
    - Infliximab ~ ¾ respond
      - Fewer complications
      - Easier to administer
      - Longterm outcomes not yet clear

  - Continue po food / fluid intake if tolerated
  - Peripheral nutrition if po intake inadequate
  - If after 3 to 5 days of trend of symptoms to remission suggested, then
    - Consult surgical service (colorectal, or very experienced general surgeon) to assess patient and follow
  - Daily
    - Abdominal examination
    - Plain abdominal film
  - Stool charting
  - Systemic corticosteroids
    - Hydrocortisone 100 mg IV q 8 h, or
    - Methylprednisolone 20 mg IV q 8 h (less fluid retention)
  - Stabilize patient
  - CBC, electrolytes, urinalysis, CRP
  - Review evidence for a diagnosis of UC vs. Crohn disease

- Review possible precipitants (eg concurrent C. difficile infection {CDI})

- Diet-as tolerated
  - Enteral (EN) or parenteral (PN) nutrition only if po cannot be tolerated.
  - EN/PN of no use to control disease activity

- NG tube only for nausea/vomiting or ileus

- Reaccess patient
  - Stool cultures C.difficile, o/p, c/s (e.g., entamoeba histolytica, Blastocystis hominis)
  - Sigmoidoscopy for UC activity, CMV (gancyclovir), C.difficile (metronidazole vancomycin), amebiasis
  - Daily abdominal examination, plus abdominal film for
    - Diameter transverse colon (> 6 cm), cecum (> 9 cm)
    - Thumb printing
    - Pneumatosis intestinalis
    - Perforation

- Anticipatory /prophylactic steps
  - Exclude TB history and physical chest X-ray tuberculin skin test QuantiFERON TB GOLD (not affected by previous BCG vaccination)
  - Serum cholesterol, magnesium, creatinine concentrations,
  - Vaccination/treatment HBV, HCV
  - Unfractionated or low molecular weight heparin prophylaxis for DVT (reassuringly, no ↑risk of gut bleeding)

- Stool charting

- Minimal use of narcotic analgesics or anti-cholinergics
- Avoid non-directed ("prophylactic" use of antibiotics), but use for proven infection or toxic megacolon
- Consultation with ostomy nurse and ostomy patient
- Informed consent re medical therapy vs. surgery, risks and benefits
  - Urgent total or subtotal colectomy with end ileostomy for megacolon, systemic toxicity, or non-response to medical therapy

- Ensure colorectal or general surgical team is aware of patient
- 5-ASAs used before admission may be stopped.
- Methylprednisolone 1.0 to 1.5 mg/kg/day, to maximum 60 mg/day, given as 30 mg IV bid, 60 mg IV od, or continuous infusion (do not exceed this dose)
- Failure to respond (CRP > 45 mg/L plus 3-8 BM/day, or BM> 8/day on day 3) to maximum 60 mg/day of methyl prednisolone within 3 to 5 days
  - prepare for "rescue therapy" ("rescue from needing a colectomy on this admission) after IV steroid failure.
    - **Cyclosporin** (2 mg/kg/day) +/- continued steroids, plus sulfamethoxazole/ trimethoprim prophylaxis for pneumocystis jirovecii pneumonia, continuous infusion for 7 to 10 days
  - If starting on cyclosporin for "rescue therapy"
    - Adjust dose to maintain trough level at 150 to 250 nanogram / mL
    - Start azathioprine 2.5 mg / kg per day
      - when cyclosporin started or
      - after 7 to 10 days if patient has responded, or
      - if patient responds to IV cysclosporine within 7 to 10 days, then
      - Switch to oral cyclosporin 8 mg / kg per day (same trough level of 150 to 250 nanogram / mL) for 3 months.
      - Begin azathioprine po 2.5 mg / kg per day, to be used as continuous maintenance therapy.
      - Begin PCP (pneumocystitis carini) pneumonia prophylaxis
  - If patient fails to responds to IV cyclosporin for 7 to 10 days
    - Then panproctocolectomy
    - Do not start IFX, after failure of cyclosporin
  - If staring on **infliximab** rescue therapy
    - Infliximab 5 mg / kg on day 0, week 2 and 6
    - May consider adding azathioprine 2.5 mg / kg per day to improve response (long colectomy-free survival)
    - Infliximab as effective as cyclosporin in severe fulminant UC, but with fewer side effects
    - If patient fails infliximab rescue therapy
      - Colectomy, if patient fails rescue therapy with infliximab, do not repeat rescue therapy with cyclosporine
- Once the patient is "out of the woods" with regards to going into remission after a severe / fulminant attack, there is still a high risk of a future severe recurrence needing colectomy.

- The outcome from colectomy is superior if performed electively.
- View rescue therapy as a means to prepare the patient for elective colectomy.
- If colectomy not performed, then
  - Maintain patient on AZA / 6-MP if started on cyclosporin, or infliximab if responding to infliximab for recent severe attack (not yet known if infliximab need to be combined with azathioprine)
  - Assess for screening / surveillance for development of dysplasia / CRC (colorectal cancer)
  - Note
    - No evidence of benefit from high doses: if no response in 3 to 5 days, prepare for "bridge" therapy with use of cyclosporin, anti-TNF therapy or urgent colectomy
- For severe UC
  - Colectomy was avoided at 3 months in ~ 2/3, and 1/2 at 3 years
  - Longterm studies not available
  - Suggest using "bridge therapy" with cyclosporin IV → po plus AZA or anti-TNF, in severe UC

- Give 8 "**alternative therapies**" for UC and CD.
  - UC
    - Phosphatidyl choline
    - Curcumin (phytochemical in tumeric)
    - Hypnosis
    - Granulocyte/monocyte apheresis
    - Probiotics
  - CD
    - Omega-3 fatty acids (DHA - and EPA-containing fish oil)
    - AST-120 oral spherical absorption carbon (for fistulae)
    - IL-12/IL-23 (ustekinumab)
    - Naltrexone
    - Probiotics
    - 4.0 to 4.8 gm/day of 5-ASA po (dose difference depends upon product choosen) for 4 weeks, then with clinical improvement reduce dose by one tablet every 3 days until maintenance dose of 2.0 to 2.4 g PO /day
    - May use both PO plus PR 5-ASA for distal disease
  - If cyclosporin (CyA) or infliximab (IFX) fail within 5 days
    - Surgery; do **not** switch between CyA/IFX (i.e., do **not** use sequential therapy)

- If CyA successful → switch from IV to po CyA (Neoral), and begin azathioprine/6-MP
  - Slow steroid taper
  - Stop CyA after between 3 to 6 months
  - Continue AZA maintenance
  - Do not resume 5-ASA therapy
- If IFX successful, continue IFX at 2 and 6 weeks, followed by IFX every 4 weeks
  - Slow steroid taper
  - Do not resume 5-ASA therapy
- Prepare patient for recue therapy ("rescue from need for urgent panproctocolectomy)
  - For cyclosporin
    - Serum creatinine
    - Magnesium
    - Cholesterol concentrations
  - For anti-TNF-α exclude TB
    - Tuberculin test
    - Chest X-ray
  - Immunizations HAV, HBV, HZV, HPV, annual flu, pneumococcus

SO YOU WANT TO BE A HEPATOLOGIST!

A 35 year old patient with UC experiences a recurrence of symptoms suggestive of active colitis, and is started on prednisolone. Two weeks later she develops suggestive of cholangitis from her UC-associated PSC, and a fluoroquinolone is started. A further three weeks later she develops fever, pharyngitis, periorbital edema, and a skin rash. The rash is not characteristic of pyoderma gangrenosa, erythema nodusum or multiforma, but is associated with severe mucositis. The liver enzymes show a mixed picture, with peripheral blood showing neutrophilia, atypical lymphocytes and eosinophils.

- Give the name of the skin rash, and of the syndrome associated with the drug reaction.
  - The onset of these symptoms and the development of these hematological abnormalities 3 weeks after starting a fluoroquinolone and steroids is suggestive of RMS (reactive metabolite syndrome),
  - The syndrome associated with the drug reaction is likely Stevens-Johnson syndrome.

- **Anti-tumor Necrosis Factor (TNF) Therapy in UC**
  - In UC, the mononuclear cells in the lamina propria produce ↑ TNF-α.
  - A TNF therapy vs placebo:
    - Failure to achieve remission 43% vs 70% RR 0.72 NNT (to achieve 1 remission), 4
    - 5 mg / kg per day – equivalent benefit as 10 mg/kg per day
    - After induction dosing of infliximab (0, 2, 6 weeks), continue dosing every 8 weeks.
    - Results of act 1 and act 2 studies (Infliximab)

Biological Therapy for Crohn Disease (CD) and Ulcerative Colitis (UC)

- Biological therapy is not to be used for
  - Fibrostenotic CD
  - Patients with active infection, abscess, or latent infection (TB, HBV, HIV)
  - Receipt of live vaccines within last 3 mon
  - Malignancy (not including non-melanoma skin cancer)
  - Lymphoproliferative disorder
  - Severe congestive heart failure or
  - Demyelinating neurologic disease
  - All septic collections should be drained before starting biologic therapy
- Patients must stop smoking
- Only some patients with CD or UC need biological therapy, including those with
  - Complex fistula, in conjunction with surgical drainage use schedules retreatment for responders
  - Inflammatory CD which is refractory to or dependent upon an adequate treatment course of steroids, or is refractory to an adequate cause of immunomodulatory therapy
- Patients with “severe disease” may be selected for early use of biological therapy, as defined by one of several categories
  - Need for (within 5 yr of diagnosis of CD)
    - 2 courses of steroids
    - Hospitalization
    - Immunomodulators
    - Surgery

- Patients losing response or becoming intolerant to one anti-TNF may respond to another anti-TNF (although the response rate nay be lower)
  - Complex perianal disease colonic resection ≥ small bowel resections within 5 yr of diagnosis of CD
- Note: because of the risk of AML (progressive multifocal leucoencephalopathy) natalizumab should not be combined with immunosuppressants, or with prolonged use of corticosteroids
- When starting biological therapy in patients not previously on thiopurines, start with IFX (infliximab) plus AZA (azathioprine)
- Predictors of good response include
  - Early inflammatory disease
  - ↑ CRP (C reactive protein)
  - High trough concentrations
  - Age < 40 early need for steroids perianal disease

Source: D'Haens et al., Am J Gastroenterol 2011, 106:199-212.

- In moderate or severe treatment-refractory UC, use IFX for induction and maintenance of remission.
- IFX may be superior to CyA (cyclosporin A) for severe UC in hospitalized patients.
- Following response to IFX for severe UC, switch to oral immunomodulator and stop anti-TNF.

	Duration of treatment, weeks	Clinical response		Mucosal healing
		Anti-TNF	PL	
○ Response	8	64% and 66%	29%	55%
- Remission	30	39% and 32%	15%	57%
○ Response	54 (durability)	45% and 44%	20%	22%
- Remission	54	34%	17%	

Abbreviation: ATNF-anti-TNF; PL, placebo

- Need for colectomy after failure to respond to IV-steroids and anti-TNF (adalimmumab) for severe UC

	Anti-TNF	PL (placebo)	TG
Within 3 months	30%	66%	36%
Within 3 years	50%	76%	26%

  - Adalimmumab (ADAL, i.e. 160 mm at week 0, 80, mg at week 2, 40 mg every second week)

	ADAL	PL (placebo)	TG
Inducing remission, wk 8	17%	9%	8%
Maintaining remission, wk 52	17%	9%	8%

Abbreviation: TG, therapeutic gain
Note: There is a greater response in ADAL naiive than in "switch (infliximab → adalimumab) UC patients

Summary

- Infliximab for UC (8 weeks)
  - Response ~ 2/3
  - Remission ~ 1/3
  - Durability of remission (54 weeks)
    - Response ~ 1/2
    - Remission ~ 1/3

➢ Debunking

- No evidence in UC for
  - Fish oil supplements
  - SCFA (short-chain fatty acid) enemas (only useful in diversion colitis)
  - Transdermal nicotine particles to maintain remission (for UC patients who smoke and have mildly active UC, using nicotine patches may be beneficial while the patient stops smoking – on no sue in UC patients who are non-smokers)
  - Heparin

- Still “on radar screen”: more data needed
  - Methotrexate
  - Budesonide MMX
  - Trichuris suis (helminthes, from pigs)
  - Oral phosphatidylcholine
  - Anti-integrin antibodies
  - Thiazolidinediones (rosiglitazone)
  - Antibodies against IL-12, IL-23
  - MAd CAM (mucosal addressin cell adhesion molecule-1)

SO YOU WANT TO BE AN IBDologist!

The thiazolidinediones (such as rosiglitazone) are used in patients with diabetes to control their hyperglycemia. There is not an increased risk of diabetes in UC, and the hyperglycemia noted in some UC patients on glucocorticosteroids is reversible.

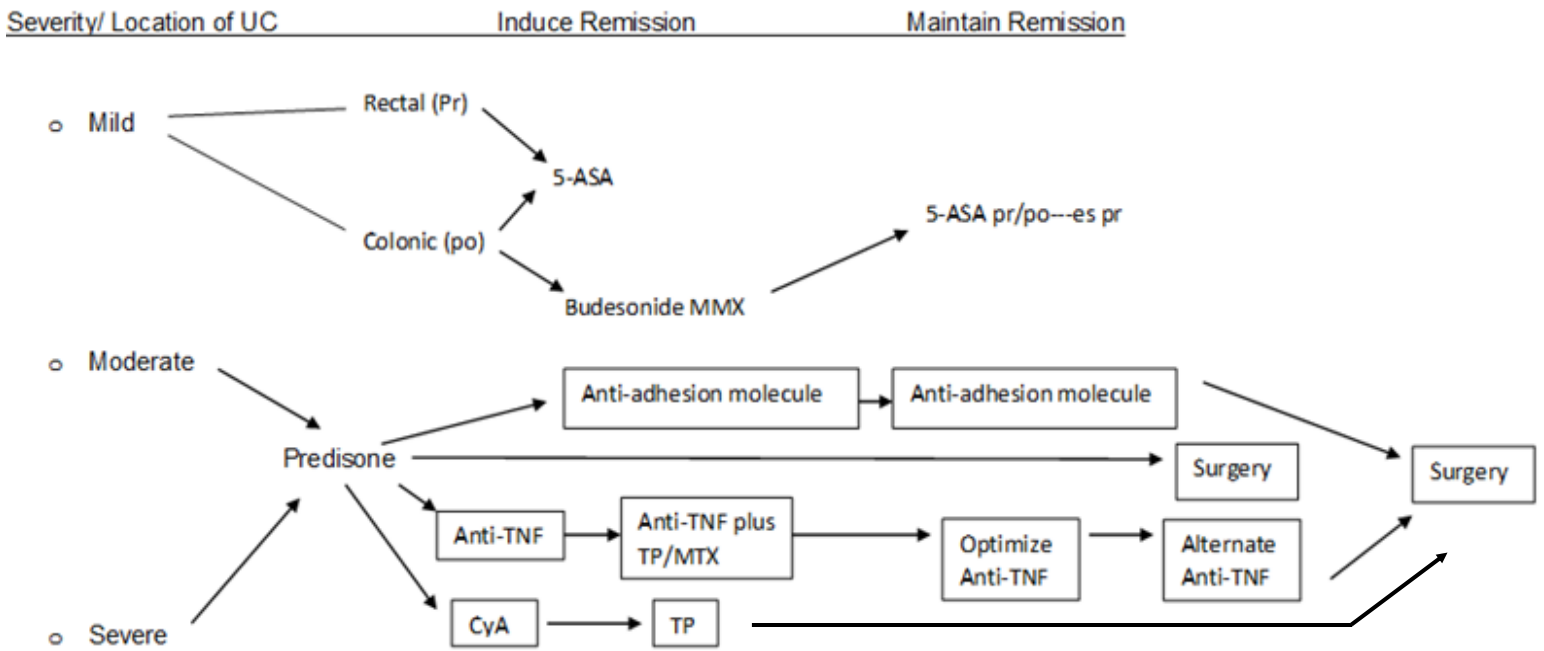
- Give the basis for explaining why rosiglitazone (a thiazolidinedione [thio]) has been shown in preliminary studies to be useful in mild-moderate active UC.
  - Thio → ↑ PPAR (peroxisome proliferator-activated receptors [or ligands]) → ↓ proinflammatory cytokines.

Clinical Alert

- Beware: if the MCQ describes the patient with longstanding UC (> 0 years), and the biopsy is reported as showing dysplasia, then the action they wish is for you to refer the patient for a possible colectomy. Now in real life there are subtle aspects that need to be assessed and considered, but this is not what you answer on MC.

Proposed Algorithm For Treatment of Ulcerative Colitis (UC)

Therapeutic Objective



PROBIOTICS

- Give 4 postulated mechanisms of action of probiotics (mostly animal studies) in diseases of the intestine.
    - ↓ pathogenic organism growth, binding or invasion of epithelium (↑ temporary colonization of probiotic species)
    - ↓ intestinal permeability (↑ TJ [tight junction] function)
    - ↑ anti-inflammatory cytokines (e.g. IL-10, TGF-B), and ↓ pro-inflammatory TNF
    - ↑ expression of receptors for opioids and cannabinoids on intestinal epithelial cells (↓ pain threshold and ↓ pain perception)
    - ↑ apoptosis mediated by an EGFR (epidermal growth factor receptor) – dependent mechanism

There are several circumstances in which probiotics might be of therapeutic benefit, but there is wide variable in the results of clinical trials of probiotics in, for example, IBD.

- Give 3 explanations for the high variability of clinical response to "probiotics".
    - There are many different microorganisms in various probiotic preparations, for example, from pasteurization.
    - The ratio (combination) of microorganisms may be as important as their numbers.
    - Some of the microorganisms in various probiotics
        - May be dead (loss of viability)
        - May be destroyed in gastric acid and fail to colonize the lumen microbiota
    - Characteristics of patients
    - Duration of studies
    - Assessed endpoints

➢ Mixed results
    - Pouchitis – VSL#3 maintenance therapy, prophylaxis

- AAD (antibiotic-associated diarrhea)
  - Saccharomyces boulardi, or Hansen CBS 5926: ↓ risk of developing AAD, RR 0.58 (↓ risk by 42%, NNT 13
  - Lactobacillus: ↓ risk of developing AAD, RR 0.64 (↓ risk by 36%)
- Infectious diarrhea, including rotavirus (minimum of 10 billion colony-forming units for first 2 days overall results, probiotics
  - ↓ duration of diarrhea by 17 to 30 hours
- Risk of Traveler diarrhea: probiotics
  - ↓ risk RR 0.85
- Crohn disease
  - Induction of remission
  - Maintenance of remission
  - Prevention of post-surgical recurrence
- SIBO (small intestine)
- Lactose intolerance
- Hepatic encephalopathy
- IBS probiotics may be helpful to ↓ bloating, ↓ flatulence, ↓ pain
- Prevention of hospital acquired C. difficile infections
- Diverticular colitis
  - Limited data for VSL #3 plus beclomethasone po
- Collageneous colitis
- Severe constipation
- Pancreatitis

- Give 4 examples of drugs used to treat IBD which have potentially serious interactions with other drugs.
  - 5-ASAs-increase INR, 6-TG and methotrexate (MTX); decreases digitalis levels
  - Allopurinol-increases 6-TG
  - ACE inhibitors-increase 6-MP-associated risk of anemia, leucopenia

- Methotrexate (MTX) levels are reduced by tetracycline, and increased by penicillin 5-ASAs and NSAIDs; folic acid deficiency worsens MTX toxicity
- Metronidazole increases the effect of statins, sildenafil, calcium channel blockers, and ↑ INR
- Anti-TNF therapy causes 6.4 fold increase in mortality rate in persons with pre-existing pulmonary disease
- Corticosteroids cause osteoporosis by changing the optimal ratio of Rank-L relative to OPG/ OCIF; this effect of steroids is greatest in the first 6 months of their use

Abbreviations: MTX, methotrexate; OCIF, osteoclastogenesis inhibitory factor; OPG, osteoprotegerin

- Give the mechanism of action of 4 treatments for **calcium oxalate kidney stones**.

➢ Fluid
- Adequate intake of water by mouth

➢ Reduce oxalate absorption
- Reduce intake of oxalate (cranberry juice, chocolate, etc)
- Oral calcium supplements to bind oxalates in the gut lumen
- Colectomy, if indicated for other reasons

➢ Increase renal excretion
- Correct metabolic acidosis

➢ Bind luminal bile acids binding agents

Wisdom is knowing what to do next; virtue is doing it.

David Star Jordan

COLORECTAL CANCER (CRC) SURVEILLANCE IN ULCERATIVE COLITIS (CRC-UC) AND CROHN COLITIS (CRC-CC)

It is generally accepted that the risk of developing colorectal cancer (CRC-Ca) in a person with ulcerative colitis

- UC is related to
  - The extent and duration of the disease
  - After 8 to 10 years of pancolitis, the cumulative risk of UC-CRC is about 0.5% to 1% per year
  - Histological severity of UC
  - Associated primary sclerosing cholangitis (PSC)
  - Possibly a family history of CRC-Ca
  - Possible history of post-inflammatory pseudopolyposis

- Give 6 features which help to **distinguish UC-CRC from sporatic CRC** (SPO-CRC).

Features	CRC-UC / CRC-UC	CRC-SPO
○ Age of diagnosis of CRC, years	40	60
○ Location of dysplasia	May be at or distant from UC／CC	Associated with polyp
○ Location of CRC	RC ~ LC	LC > RC
○ Mutation		
– RAS protooncogene		
▪ %	~ 20%	50%
▪ Timing	Late	Early
– LOH for p53		
▪ Timing	Early	Late
▪ In non-dysplastic tissue	Yes	No
– SRC activation		
▪ Timing	Early	Late
▪ Correlate with degree of dysplasia	Yes	No
○ Pathology		
– Anaplastic	Often	Less often
– Mucinous	Often	Less often
○ Synchronous	more common in UC-Ca than in SPO-Ca	

Abbreviations: CC, Crohn colitis; CRC-CC, colorectal cancer in a patient with UC; CRC-UC, colorectal cancer in a patient with UC; LOH, loss of heterogeneity; RC, right colon; LC, left colon

Biopsies of the colon taken for dysplasia / CRC surveillance in a patient in the UC ideally should be taken when the UC is inactive (i.e. in remission).

- Give the influence of male gender on the risk of UCCRC after 10 years of pancolitis.
    - The risk of UC-CRC is higher in males than females (8% vs 3% after 40 years of disease)
    - This male-effect is seen only in males diagnosed with UC before age 4 years.

- Give 6 histopathological features which help to **distinguish dysplasia from regenerative changes** in active UC.

The following are histopathological features which suggest dysplasia

- Architectural
    - Back-to-back gland pattern
- Cytological
    - ↑ stratification of nuclei
    - ↑ nuclei size
    - ↑ pleomorphism (variation in size and shape)
    - ↑ ratio of nuclei / cytoplasm
    - ↑ mitosis (typical atypical)
    - Altered polarity of nuclei
    - ↑ chromaticity (hyperchromaticity)

We are made wise not by the recollection of our past, but by the responsibility for our future.

George Bernard Shaw

Features	Dysplasia	Regenerative changes
○ Changes in		
– Crypts	Yes	Yes
– ↓ Surface epithelial maturation	Yes	No
○ Positive tissue IHC for		
– AMACR	Yes	No
– Sialosyl-TN	Yes	No

Abbreviations: AMACR, alpha-methyl-acyl-CoA-racemase (a mitochondrial and peroxisomal enzyme with ↑ expression in dysplasia); IHC, immunohistochemistry

SO YOU WANT TO BE A GASTROENTEROLOGIST!

The current guidelines suggest that four quadrant mucosal biopsies every 10 cm from cecum to rectum must be taken when colonoscopy is performed for CRC surveillance in UC or CC (Crohn colitis), as per standard guidelines such as those recommended by ACG, ASG, BSG, CDG. Areas of mucosal irregularity should also be biopsied.

- Give the number of colonic mucosal biopsies which need to be taken at the time of colonoscopic surveillance for persons with chronic UC or CC, in order to detect dysplasia with 90% confidence.
  - Thirty-three (33)
  - Now ask the patient if she/he is satisfied to wait 1 to 2 years for their next colonoscopy with biopsies, with the chance that the dysplasia miss rate is at least 10% (and as high as 70%), and the risk of their already having a missed CRC is 19% to 33%.

A patient with chronic distal UC for 30 years is found to have a polypoid lesion at the junction of the UC and non-UC mucosa.

- Give 8 features which help to **distinguish a non-adenoma-like DALM** (dysplasia-associated lesion or mass) from a **sporatic adenoma** (SPO-Ad).

Feature	DALM	SPO-Ad
○ Patient		
- Age of patient	Younger	Older
- Duration of UC	Longer	Shorter
- Extensive	More	Less
- Size of lesion	Larger (~ 18 mm)	Smaller (~ 5 mm)
- Endoscopic appearance of lesion	Large Plaque Ulcerated	Pedunculated, or Sessile
○ Molecular markers		
- Beta catenin	8%	40%
- P53	29%	5%
○ Treatment		
- HGD	Prompt colectomy	Polypectomy, plus post-polypectomy surveillance
- LGD	Controversial (see below)	

Abbreviation: HGD, high grade dysplasia; LGD, low grade dysplasia

- It is controversial whether the patient with low grade dysplasia (LGD) should also have prompt colectomy, or have continued intense surveillance with multiple biopsies.
- When given the following statistics (M. A. Peppercorn and RD Odze, UpTo date May 2012), many patients will choose to have colectomy, rather than colonoscopy plus biopsy performed at least once per year with quadrant biopsies every 10 cm from cecum to rectum.
  - ~ 70% of UC and ~ 30% of CC (Crohn colitis) already have dysplasia in a portion of the colon.
    - 19% to 33% already have CRC (colorectal cancer)
    - 34% will have CRC in 1 year

- Progression
  - 50% LGD → HGD / CRC
  - 15% LGD → CRC in 10 years

Note:

- The BSG (British Society of Gastroenterology) but not the AGA / ASG (American Gastrointestinal Association / American Society of Gastroenterology) guidelines suggest that surveillance in Crohn colitis (CC) may be every 5 years, rather than more frequently, if their CC involves < 50 cm of the colon.
- It is possible that 5-ASA, folic acid, calcium, ASA, or NSAIDs may reduce the risk of sporadic CRC, as well as CRC associated with IBD.
- There is no evidence that azathioprine, 6-MP or anti-TNF therapy reduces the rate of development of IBD-associated dysplasia / CRC.

SO YOU WANT TO BE A GASTROENTEROLOGIST!

It may be difficult to distinguish dysplastic from regenerative mucosa in IBD. For this purpose, several markers have been developed, such as Ki-67, p53, sucrase isomaltase and Sialyl-Tn antigen.

- Give the characteristics of AMACR (α-methylacyl-CoA racemase) which make it a promising diagnostic marker for dysplasia in IBD.
  - Specificity > 99%
  - Sensitivity
    - LGD • 96%
    - HGD • 80%
    - Adenocarcinoma • 71%

A combination of immunohistochemistry for AMACR and histopathological evaluation is useful.

- Give the performance characteristics of these fecal tests for colonic adenomas and CRC.
  - FOBT (fecal occult blood test, guaiac-based relying on the peroxidase reaction)
    - Only adenomas > 1.5 cm bleed and thus FOBT sensitivity depends on the size of the lesions in the test group
    - False negative for adenomas, 75%
    - False positive (red meat, vegetables containing peroxidases [e.g. horseradish])
    - PPV (positive predictive value): adenomas, ~30%; CRC, ~10%
  - FIT (fecal immunochemical testing for human globin)
    - Sensitivity (advanced adenomas), 25%
    - Specificity (adenomas), 97% (93% for advanced adenomas)

PYODERMA GANGRENOSUM (PG)

- Definition:
  - An ulcerative skin condition associated with accumulation of neutrophils in the skin lesions.
  - Symptoms may be out of proportion to size / appearance of PG lesion
  - May be severe

- Give the treatment of PG (pyoerma gangrenosum)
  - Use a combination of topical and systemic therapy
    - Moist dressing
      - Zinc oxide, petrolatum to protect surrounding skin and prevent pathergy (worsening of lesions at sites of trauma)
  - Local
    - Glucocorticosteroids
      - Superpotent topical steroids for 1 to 2 times per day, 2 to 3 weeks
    - Calcineurin inhibitor (cyclosporin, tacrolimus, 0.3%)
  - Systemic

- Dapsone 50 to 200 mg po per day
- Minocycline
- Steroids
- Cyclosporin 4 to 5 mg/kg per day, slow taper
- Infliximab 5 mg/kg, single dose
- Adjunct therapy with
  - Azathioprine
  - Methotrexate 10 mg to 30 mg per week
  - Mycophenolate
  - Mofetil 2 g to 3 g per day
- IVIG IV immunoglobulin
- Alkylating agents
  - Cyclophosphamide 500 mg/m^2, IV, once per month or 6 months
  - Chlorambucil 2 mg to 4 mg per day (± prednisone)

- Hyperbaric O_2
  - Skin
    - Careful debridement
    - Skin flaps
    - Skin grafts
    - Bioengineered keratinocyte autografts
  - Consider subcuticular stitiches
  - Colon
    - PG does not follow the activity of UC, so colectomy does not usually improve PG

- Treat associated condition
  - IBD (UC, CD)
  - Arthritis
  - Hematologic malignancy
  - Prognosis: overall,
    - 6 month 68%
    - 12 months 95%

} Remission, all treatments

- Give 3 indications and one major contraindication for the use of **dapsone** in gastroenterology.
  - Indication
    - DH, dermatitis herpetiformis
    - PG, pyoderma gangrenosa
    - MAC infection
    - Leprosy
  - Contraindication
    - G-6-PD (glucose-6-phosphhate dehydrogenase) deficiency

POUCHITIS

- Give the features which distinguish acute and chronic pouchitis after IPAA (ileal pouch anal anastomosis) for UC.

Feature	Acute	Chronic
Incidence (% per year)	~ 4%	3%
Risk factors	Preoperative use of steroids Smoking	Preoperative thrombocytosis Extraintestinal associations ↑ length of follow-up
Serology		Low pANCA plus anti-CBir 1 High pANCA

  - Complications may develop in the pouch after proctocolectomy and IPAA (ileal pouch-anal anastomosis)
  - Prevalence
    - When IPAA is done for UC
      - 7% to 44%
    - When done for FAP
      - < 1%

- For UC
  - Year 1 ~ 20%
  - Year 5 ~ 50%
- Microbiota in pouchitis (unique pattern)
  - ↑ Clostridium perfringens
  - ↓ Streptococcus sp (species)
  - Unchanged Fusobacteria
- Treatment results of probiotics (VSL #3, 3g / day) in pouch + IPAA

	VSL #3	PL	TG
– Development of pouchitis after IPAA	10%	40%	30%
– Maintenance of remission induced by antibiotics	85%	6%	79%

		VSL #3	PL	TG
– Induction of remission	6 weeks	33%	10%	23%
	12 weeks	43%	16%	27%

	VSL #3 + 5-ASA	5-ASA (balsalazide)
– Maintenance of remission	73%	21%

Abbreviations: PL, placebo; Pro, probiotic; TG, therapeutic gain

- Give 5 factors which contribute to the wide variation in the prevalence biopsy-proven pouchitis.
  - Clinical severity

	Months after IPAA		
	6	12	48
– Mild	21	26	39
– Severe	9	11	14

  - Extensive colitis pre IPAA
  - Use of steroids pre IPAA
  - Use of NSAIDs
  - PSC (primary sclerosing cholangitis)

- Serology
  - NOD_2 / CARD 15 gene mutations (60% vs 5% asymptomatic NOD_2 / CAR15-negative UC patients post IPAA
  - pANCA (perinuclear cytoplasmic antibody) positive (higher risk with higher pANCA titre)
- Pathology
  - Multiple biopsies must be taken from the mucosa of the reservoir (pouch) – suggestion, 6
  - Abnormalities present in 95%
  - Inflammation degree
    - Mild, 56%
    - Chronic, 39%
  - Partial colonic metaplasia
    - 35% to 96%
- Clinical course
  - Recurrent episodes of pouchitis, 50%
  - Chronic symptoms (> 4 weeks), 10% to 20%

Clinical Caution

- Pouchitis with IPAA for UC has numerous complications. If the pouchitis is severe or if mucosal biopsies show persistent atrophy, endoscopic, surveillance plus biopsies must be annually
  - With mild pouchitis and no atrophy, sigmoidoscopic surveillance with multiple biopsies should be performed q 3 years to q 5 years.
- If UC patients have had a colectomy, have an ileostomy and the rectum remains in place, sigmoidoscopic surveillance with multiple biopsies should be performed q 3 years to 5 years.

- Give 4 **predictive factors** for the development of pouchitis.
  - Positive association
    - Extraintestinal manifestations
    - Primary sclerosing cholangitis
    - Antineutrophil cytoplasmic antibody with a perinuclear staining pattern (p-ANCA)
    - Extent of preoperative UC
  - Negative association
    - Smoking

Printed with permission: Gionchetti P, et al. *Best Pract Res Clin Gastroenterol* 2004;18(5): 995.
A patient has an ileoanal pouch (IAPP) after proctocolectomy for UC.

- Give differential diagnoses for **late pouch-related symptoms**.

  - Pouch
    - Cuffitis
    - Irritable pouch syndrome
    - Adhesions
    - Stricture
    - Abscess
    - Pelvic floor dysfunction
    - Late anastomotic leak
    - Malignancy (squamous cell cancer) of anus, small bowel cancer
  - Small intestine
    - Crohn disease
    - NSAID-induced damage (especially with isolated afferent limb ulcers)
    - Poor reservoir capacity
    - Small intestinal bacterial overgrowth syndrome (SIBO)
    - Unmasked celiac disease
    - Unrelated conditions, including infections

➢ Treatment

- Give the treatment of pouchitis in patient with IPAA for UC.

  - Antibiotics
    - Ciprofloxacin 500 mg bid, for 7 days
    - Metronidazole 500 mg to 1 gm po bid, for 7 days
      - Because of AEs of 33% vs 0% for cipro', use as second choice for when cipro' fails)
    - For the 50% of patients with recurrent episodes of pouchitis, use the antibiotic to which they previously responded
    - For those who have frequent recurrent symptoms or chronic symptoms and maintenance therapy is considered, use lowest useful dose of cipro' or metronidazole, or rifamximin (useful in 65% of chronic pouchitis patients, but not useful

to induce remission), or use probiotic maintenance (please see below)

- Steroids
  - Budesonide
    - 9 mg po per day for 8 weeks
    - Used for pouchitis patients who fail treatment with antibiotics
    - Budesonide suppositories or enemas may also be therapeutically effective
  - Glucocorticoid enemas or tablets (including foams)
- Probiotics
  - VSL#3
    - Continuously for maintaining remission (85% remission at 1 year versus 6% to 15% for placebo)
- Mesalamine enemas
- Infliximab
  - For refractory pouchitis, or pouchitis associated with fistulae
  - May be useful for maintenance
- Immuno-suppressants
  - Azathioprine, 6-MP for maintenance
- Cancer surveillance
  - Partial colonic metaplasia in 35% to 96%
  - Mucosal atrophy and dysplasia may develop
  - Dysplasia / cancer is more common if there is a remnant rectal cuff
  - Sigmoidoscopy with multiple biopsies q 3 years
  - If biopsies show atrophy, then sigmoidoscopy plus multiple biopsies q 1 year

SO YOU WANT TO BE A CLINICAL TRIVIOLOGIST!

About 99% of flatus is comprised of N_2, O_2, H_2, CO_2 and CH_4. Two of these are flammable, H_2 and CH_4. Increased H2 in the breath may reflect SIBO (small intestinal bacterial overgrowth), and CH4 is also a product of luminal bacterial metabolism. Increased levels of breath methane may be found in persons with constipation.

- Give the name of the main methanogenic bacterium in the human intestinal tract.
  - Methanobrevibacter smithii. Doesn't it make you happy to know this!

Now here's another winner: there are many causes of bloating, one of which is known as functional bloating. Naturally, this has been a topic of learned discussion by the Rome group, which has created a concensus criteria for functional bloating.

- Give the Rome III concensus criteria for the manner in which functional bloating may be distinguished from other causes.

  - Functional bloating has a diurnal pattern

PNEUMATOSIS CYSTOIDES INTESTINALIS

- Definition
  - Gas-filled cysts in the wall of the bowel, thought to rise from idiopathic ↑ H_2 in the bowel lumen
- Treatment
  - ↓ intake of carbohydrates
  - Metronidizole to reduce any associated bacterial overgrowth
  - Inhaled O_2 for at least 48 hours
  - Resection for haemorrhage or obstruction of colon

DIVERTICULAR DISEASE

Acute Diverticulitis

- Definition
  - Uncomplicated
    - Accounts for 75%
    - About 30% require surgery (success rate of antibiotics and no surgery, 70% to 100%)
    - Localized infection
  - Complicated
    - Accounts for 25%
    - > 95% require surgery
    - Complications
      - Hemorrhage
      - Obstruction
      - Perforation
        - Fistula
        - Abscess
        - Peritonitis
- Organisms
  - Gram-negative rods
  - Anaerobics (E. coli, B. fragilis)
- Treatment

- Overview
  - Antibiotics
    - Organisms
      - E. coli
      - Streptococcus
      - Bacteroids fragilis
    - Metronidazole / clindamycin plus aminoglycoside / cephalosporin

- Uncomplicated diverticulitis
  - Diet / fluids
    - IV fluid balance
    - Begin NPO / clear fluids, advance as tolerated to normal diet
    - No specific dietary therapy needed (including seeds, nuts, popcorn)

○ Ciprofloxacin 500 mg po bid, plus	-	Metronidazole 500 mg pot tid, or
	-	Amoxicillin-clavulanate, or
○ Metronidazole 500 mg po bid, plus	-	Trimethoprim-sulfamethoxazole 875/125 mg po bid for 10 to 14 days
○ Clindamycin	-	In place of metronidazole for intolerance of metronidazole
○ Moxifloxacin	-	May be used in place of beta-lactam-beta-lactamase inhibitor, e.g. amoxicillin-clavulanate

- ○ Success rate 70% to 100% (0% to 30% require surgery)
- ○ Post recovery investigations
  - Guidelines as to CRC screening and surveillance
  - If symptoms of diverticulitis occur between interval for surveillance colonoscopy, perform interval colonoscopy
- ○ Natural history after successful medical therapy after first episode of uncomplicated diverticulitis, at 5 years
- ○ After # 1 attack
  - 1/3 remain asymptomatic
  - 1/3 intermittent cramps, no diverticulitis
  - 1/3 → #2 attack of acute diverticulitis → 4% complicated diverticulitis → MR 1.3% to 5%

- Recurrent diverticulitis
  - ○ ~30% have second episode of diverticulitis, ½ within one year
  - ○ "multiple recurrences don't appear less-favourable outcomes" (Feldman M., et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. Saunders/Elsevier, Philadelphia, 2010, page 2083).
  - ○ "a recent decision analysis predict that performing colectomy after the fourth attack of diverticulitis rather than after the second attack would result in fewer deaths and colostomies while having a superior cost-effectiveness" (Feldman M., et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. Saunders/Elsevier, Philadelphia, 2010, page 2083).
  - ○ Unfortunately, patients who have had a surgical resection
    - Recurrent diverticulitis, 10%
    - Further surgery, 2% to 3%

- Endoscopic dilation +/- stent for stricture
- Surgery
  - Required in ~25%
  - Uncomplicated bowel preparation
    Single-stage resection
  - Complicated
    - Two stage resection, end colostomy, oversewing distal stump (Hartmann procedure); reanastomosis)
  - Fistula (colovesical, colovaginal
    - Single stage resection

- After surgical therapy for diverticulitis
  - 15% develop new diverticula
    - 5% require further surgery
    - 27% develop recurrent pain but no diverticulitis
    - 5% "smoldering" diverticulitis: LLQ pain, altered bowel habit, bleeding for > 6 mon
    - Eventual resolution of symptoms in 77%
    - Distinguish from "IBS" and recurrence of symptoms from diverticular disease
    - Further resection colonic may be necessary

Clinical Gem

The requirement for surgery in the patient is clear if there is a free perforation, non-drainable (percutaneous) abscess (septic focus), or to treat hemorrhage, obstruction or fistula.

There needs to be individualization of when / if to perform surgery for the second or third uncomplicated diverticulitis attack

However, if the patient is immunosuppressed, consider elective surgical resection of diverticula with a lower threshold; because

- Often few symptoms or signs to suggest perforation
- ↑ risk of perforation
- ↓ success of medical therapy

	Non-immunosuppressed	Immunosuppressed
Success	76%	0%

- Exceptions
  - HIV / AIDS patients responding to HAART
  - Short course chemotherapy (important to start chemo' and not to have to delay chemo' for recovery from elective colonic resection)

- Complicated diverticulitis
  - Use IV form in place of po until patient is stable, then po for 10 to 14 days
    - Ampicilin-sulbactam 3 g IV q 6 h, or
    - Piperacillin / azobactam 3.315 g IV q 6 h, or
    - Ticarcilin-clavulanate 3.1 g IV q 6 h
    - Ceftriaxone 1 g IV q 24 h, plus metronidazole 500 mg IV q 8 h
  - For beta-lactam intolerance use
    - Ciprofloxacin 400 mg IV q 12 h, or
    - Levofloxacin 500 mg to 750 mg IV q 24 h, pus metronidazole 500 mg IV q 8 h, or
    - Imipenem 500 mg q 6 h
    - Meropenem 1 g q 8 h
    - Ertapenem 1 g q 24 h
  - CT-guided percutaneous drainage of abdominal abscess(es)
  - Once cultures are returned and susceptibility is known, change regimen accordingly
  - Treatment of complications
    - Perforation
      - Mortality rate
        - Purulent peritonitis 6%
        - Fecal peritonitis 35%
        - Free intraperitoneal rupture 25%
    - Penetration (abscess)
      - Prevalence if
        - No surgery needed, 16%
        - Surgery needed, 31% to 56%
    - With CT-guided percutaneous drainage and catheter drainage
      - Depends on Hinchey classification

Hinchey classification of diverticular penetration / perforation (Stages)

I	Pericolic abscess Mesenteric abscess
II	Walled-off pelvic abscess
III	Generalized, purulent peritonitis
IV	Generalized, fecal peritonitis

- Stage I and II
  - Pre-operative bowel preparation
  - 1-step surgical procedure (primary anastomosis)

- Stage II and III
  - No pre-operative bowel prep'
  - 2-step surgical procedure e.g. Hartmann procedure

  #1 -
  - Resection of colon with diseased diverticula
  - End-colostomy
  - Creation of rectal stump

  #2 -
  - Colostomy closure (~ 3 mon later)
  - Or alternative approach
    - No purulent or fecal peritonitis
    - Still relative contraindications to primary closure

  #1 -
  - Resection
  - Primary anastomosis
  - Colostomy or ileostomy

  #2 -
  - Closure of stoma

- Elective 1-stage surgery is possible in 60% to 80%
- Otherwise, 2-procedure surgery free-
  - Fistula
  - Perforation / peritonitis
  - Adhesion of adjacent bowel loops
  - Recurrent abscesses
  - > 3 cm abscess
  - Continue symptoms > 3 days

- Age extremes
  - Younger
    - More frequent need for surgery because of more severe and more recurrent disease
  - Older
    - Less frequent need for surgery, less recurrent disease, but because of more frequent comorbidities in elderly, surgical morbidity is more
  - Treatment of the immune-suppressed (IS) patient (risk of complication, %)

Complication	IS	Non-IS
- Perforation	43	14
- Need for surgery	58	33
- Post-op mortality	39	2

  - Note
    - The post-operative mortality rate in persons with a solid organ transplantation who develops diverticulitis is very high (25% to 100%)

➢ Risk factors
  - Retroperitoneal abscess in attack #1
  - > 5 cm colon involved in attack # 1
  - Family history of diverticulitis
  - Uncomplicated diverticulitis
    - Attack #2 or #3 may be treated surgically to avoid further episodes of diverticulitis
    - After #2 attack → 1/3 develop attack # 3
  - Laparoscopic (Lap) resection best for
    - Resolved diverticulitis
    - Hinchey classification I or II disease
    - Fewer complications

	RR Lap vs. Open resection
o Wound infections	1.85
o Blood transfusions	4.0
o Ileus	2.70
o Incisional hernias	3.70

Clinical Pearl

The localization of diverticula and site of those with diverticulitis varies remarkably with geography: in Asia, disease is more common on the right side

	Non-Asian	Asian
○ Diverticular disease	5%	20%
○ Diverticulitis	1.5%	75%

Clinical Cautions

In the patient with complicated diverticulitis, if blood cultures show "recovery of more than one organism should suggest polymicrobial infection including anaerobes, even if no anaerobes are isolated in culture. In such circumstances, anaerobes coverage should be continued" (T Young-Fadok and JH Pemberton, UpToDate Nov 2011)

COLONIC POLYPS AND NEOPLASIA

- Definition: "A gastrointestinal polyp is a discrete mass of tissue that protrudes into the lumen of the bowel" (Feldman M., et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. Saunders/Elsevier, Philadelphia, 2010, page 2155).

Caution: An adenoma is neoplastic, because it shows low grade cellular dysplasia.

- Demography
  - Age 50, asymptomatic, average risk
    - Likelihood of finding
      - Adenomatous polyp, ~30% (5:3 M to F)
      - AAA (adenoma with advanced pathology, ~8%)
    - Greater risk of large or right-sided adenoma in African Americans > 60 years
    - Adenoma recurrence, 19% per year
    - Incident
      - Adenomas, 5% per year
      - AAP, 0.4% per year

- Terminology
  - AAP (advanced adenomatous polyps, aka adenoma with advanced pathology)
    - Villous architecture, or
    - High grade dysplasia (HGD), or
    - > 1 cm
  - Aberrant crypts
    - Small, raised foci of irregularly-shaped crypts when viewed from lumen by magnifying endoscopy
    - Hyperplastic or adenomatous (when adenomatous, are preneoplastic)
  - Deminative polyp
    - ≤ 5 mm
  - Flat adenoma
    - Flat, or slightly raised
    - May be multiple
    - D > 2x T (diameter [D] is more than two times the thickness [T]) of the lesion
    - Usually < 10 mm (T < 5 mm)
    - Represent ~10% of adenomas (% depends on techniques used for detection, e.g. chromoendoscopy shows that 7% to 36% of all adenomas are flat!)
    - More HGD / cancer risk
  - Serrated adenomas
    - Histopathological features for both adenomatous plus hyperplastic polyp

Comparison of traditional serrated adenomas (TSA) and sessile serrated adenomas (SSA)

- TSA
  - Often protuberant
  - Infrequent
  - Dysplastic
  - Distal colon
- SSA
  - Sessile or flat (subtle)
  - Proximal
  - BRAF mutation
  - CpG island methylator phenotype
  - Microsatellite instability
- "Multiple". e.g. multiple polyps or multiple CRCs ≥ 2

- Synchronous
  - Two polyps or one identified at the same time e.g. the index polyps is seen in the descending polyps, and a second polyps seen in the cecum at the time of the same colonoscopy
  - About 40% of colons with one polyp will have ≥ 1 synchronous polyps
- Metachronous
  - A polyp or CRC is identified at the index colonoscopy, and a polyp or CRC identified six months later is metachronous.
- Malignant
  - "the term malignant polyp refers to an adenoma in which a focus of carcinoma has invaded beyond the muscularis mucosae into the submucosal" (Feldman M., et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. Saunders/Elsevier, Philadelphia, 2010, page 2169).
  - Note that some non-adenomatous polyps (e.g. hamartoma, juvenile [when polyps are multiple]) may also become malignant (i.e. the above definition refers to "adenoma", but when non-adenomatous polyps develop CRC, they are still referred to as being "malignant".
  - Colonic cancers which have a polypoid appearance may also be called a "malignant polyp".
  - About 5% of adenomatous polyps
- Mucosal
  - Submucosa pushes mucosa to appear as a small bump
  - Seen in ~10% of screen colonoscopies
  - No clinical importance
- Inflammatory
  - Inflammation and granulation tissue resulting from regeneration of ulcerative tissue
- Juvenile
  - ↑ lamina propria, with edema
  - Dilated cystic glands filled with mucus
  - Inflammatory cells
  - ↑ vascularity
- Peutz-Jeghers
  - "hamartomatous lesion characterized by glandular epithelium supported by an arborizing framework of well-developed smooth muscle that is contiguous with the muscularis mucosae" (Feldman M., et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. Saunders/Elsevier, Philadelphia, 2010, page 2175).

- Give a classification* of colorectal polyps.
  - Neoplastic
    - Adenoma
    - Carcinoma
  - Non-neoplastic
    - Hyperplastic
    - Mucosal polyps
    - Juvenile
    - Inflammatory
  - Hamartomas
    - Peutz Jeghers syndrome (PJS)
    - Juvenile polyps

- Another useful classification of colorectal polyps

➢ Mucosal lesions
  - Adenoma
    - Tubular
    - Tubulovillous
    - Serrated villous
  - Carcinoma
    - Carcinoma in situ
    - Intramucosal
  - Invasive
  - Hyperplastic
  - Inflammatory
  - Juvenile (retention)
  - Peutz-Jeghers (hamartomas)
  - Normal mucosa in a polypoid configuration

➢ Submucosal Lesions
  - Colitis cystica profunda
  - Pneumatosis cystoides intestinalis
  - Lymphoid polyp (benign and malignant)
  - Lipoma
  - Carcinoid
  - Metastic neoplasms

Adapted from: Itzkowitz, Steven H. and Rochester, Jeremy. *Sleisenger & Fordtran's gastrointestinal and liver disease: Pathophysiology/Diagnosis/Management* 2006: pg. 2714.

- And a futher alternate approach to a classification of colonic polyps
  - Epithelial cells
    - Adenomatous, hyperplastic, serrated
    - Mucosal
    - Inflammatory
  - Hamartomas
    - Juvenile
    - Peutz-Jeghers syndrome
    - Cowden disease
    - Bannagan Ruvalcaba Riley (BRR) syndrome
    - Neurofibromatous
  - Submucosal
  - Colitis cystica coli
  - Pneumatosis cystoides coli

*based on predominant glandular pattern (may be mixed, e.g. serrated adenoma)

- Pathology
  - Adenoma
    1. Immature goblet or columnar cell
    2. ↑ cellular of crypts
    3. ↑ mucin
    4. ↑ hyperchromatic (↑ basophilia)
    5. Elongated nuclei
    6. "picket fence" pattern of nuclei

- Give the **histopathological findings** of mild, moderate and severe dysplasia.

Feature	Mild (70%)	Moderate (20%)	Severe (5%)
Nuclei	– Basal position – Hyperchromatic – Elongated – Elongated – Uniform size	Stratified Pleomorphic	↑↑ ↑↑
N/C ratio	– Ratio	Normal	↑
Nucleoli	– Normal	Normal	↑↑
Cribriform**	-	+/-	+
Mucin	↓	↓↓	

Feature	Mild (70%)	Moderate (20%)	Severe (5%)
○ Distribution of changes in crypt	– Partial	Entire	Entire
○ Architecture	– Branching – Budding – Crowding	↑	↑↑↑

*cribriform appearance, aka glands within glands

Abbreviations: HGD, high grade dysplasia; LGD, low grade dysplasia; N/C ratio, ratio of nucleus to cytoplasm

- ○ Note:
  - – Common practice > LGD -- includes mild plus moderate dysplasia
    > HGD -- includes severe dysplasia plus carcinoma in situ
  - – The agreement between even expert pathologist of the diagnosiss of LGD vs. HGD is poor (low [k] kappa value)
- ○ Recall that
  - – If an adenomatous polyp has HGD, cancer, or a villus architecture, it is considered to meet the criteria for being called an AAP (adenoma with advanced pathology)

- Give the histopathological terms used to describe non-invasive versus invasive colonic cancer.

Name	Through basement membrane	Into lamina propria	Through muscularis mucosae
○ Non invasive carcinoma in situ	-	-	-
○ Intramucosal cancer	+	+	-
○ Invasive malignant polyp	+	+	+

SO YOU WANT TO BE A GASTROENTEROLOGIST!

- Give the anatomical reason why carcinoma in situ and intramucosal carcinoma are considered to be non-invasive lesions, with no potential to metastasize.
  - Carcinoma in situ and intramucosal cancer of the colon are contained in the mucosa, which lacks lymphatics, and thus there is no potential to metastasize.
- Give the histopathological characteristics of an AAP (adenoma with advanced pathology):
  - AAP are adenomatous polyps which have one or more of the following:
    - Villous architecture
    - Presence of high grade dysplasia
    - Carcinoma

  - Size: Of course colonic polyps come in all sizes, but for purposes of considering their malignant potential, they are categorized as
  - Diminutive < 5 mm, about
    - 1/3 to ½ have adenomatous changes
    - 0.1% have carcinoma
  - Small > 0.5 < 1 cm
  - Medium 1 to 2 cm
  - Large > 2 cm

Clinical recommendation:

Rather than using an adjective to describe the size of a polyp in a colonoscopy dictation (e.g. small, medium, large), give the actual estimated size.

- Give the value of detecting a distal polyp for estimating the approximate frequency of a synchronous adenoma with advanced pathology (AAP; advanced adenoma [AA], predictive value).
  - ↑ with size of distal polyp
  - Varies with histopathology of distal polyp

Distal colonic lesion	AA*
– No polyp	3%
– Hyperplastic	3%
– Adenoma	1%
– Advanced adenoma (AA)	
▪ Tubular > 1 cm	9%
▪ Villous	12%
▪ HGD	12%
▪ Cancer (invasive)	25%

Note:

- Only 30% of proximal CRC have a distal colonic marker lesion, and
- Only half of persons with proximal advanced adenoma (AAP) have a distal marker

Adapted from: Feldman M., et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. Saunders/Elsevier, Philadelphia, 2010, Table 122.9, page 2169.

- What is the possible use of all of this information?
  - If you do sigmoidoscopy for CRC screening and an adenomatous polyp is found, you have an estimate of the likelihood of finding a second and more proximal lesion, were a colonoscopy to be now performed.
  - But because many proximal lesions do not have a distal marker, you really should be arranging for your patient to have colonoscopy, regardless of what the distal colon shows.

- Give the postulated progression of colonic mucosa to sporatic adenoma

○ Normal crypt	– Proliferative compartment at the base of the crypt
↓	
○ Aberrant crypt	– Expansion of proliferative compartment to entire crypt
↓	
○ Unicryptal adenoma	– Monoclonal expansion
↓	
○ Sporatic adenoma	– Polyclonal expansion

SO YOU WANT TO BE A GASTROENTEROLOGIST!

- On the basis of performance characteristics, give the reasons why air contrast barium enemas (ACBE) are being used less and CTC (CT colography) is being used more than standard white-light optical colonoscopy (WLOC) for the detection of colonic adenomatous and polyps.

Approximate detection rate and polyp size

	Small < 6 mm	Medium 6 to 10 mm	Large > 10 mm
○ ACBE False positive, 10% False negative, 10%	32%	53%	48%
○ WLOC	80%	88%	95%
○ CTC	45%	78%	90%

○ Human DNA in stool

	Sensitivity	Specificity
Adenoma > 1 cm	59%	-
Carcinoma	83%	82%

- ○ Annual FOBT (slide guaiac test for pseudoperoxidase activity of hemoglobin) results in 33% ↓ CRC mortality as compared with non-tested control group
- ○ Fecal immunochemical tests (FIT) are preferred over guaiac-based fecal occult blood tests for CRC screening
- ○ In a validation experiment performed at room temperature, conversion of test outcomes only occurred 10 days or longer after fecal sampling

Source: Van Roon AHC, et al. Am J Gastroenterol 2012; 107: 99-107.

In pursuit of trivia

- Give the approximate ↑ risk of colorectal cancer in the person with Cronkhite Canada syndrome.
  - ○ No ↑ risk of CRC (colorectal cancer)

SO YOU WANT TO BE A GASTROENTEROLOGIST!

- Give 5 colonoscopic (gross) features which distinguish between an adenoma-like endoscopically resectable DALM and a non-adenoma-like endoscopically non-resectable DALM.

Colonoscopic features	Adenoma-like	Non-adenoma-like
○ Shape	Sessile/ Pedunculated	Sessile
○ Borders		
– circumscribed	Yes	No
– clearly visible	Yes	No
○ Surface	Smooth	Irregular
○ Ulcer/necrosis	No	Yes
○ Stricture	No	Yes
○ Tethering of mucosa	No	Yes

- **Post-polypectomy Colonoscopic Surveillance**
  - In order to determine when a respect colonoscopy needs to be performed after an initial procedure is free of polyps or shows polyp(s) which may recur, it is important to know the natural history of polyps, i.e. when polyps may occur after the index colonoscopy.
  - For 1 cm polyps (histology unknown), the cumulative risk of carcinoma (Ca) developing is approximately 1% per year:

Time interval, years	Risk of Ca developing
5	2.5%
10	8%
20	24%

  - For a polyp < 0.5 cm, it takes 2 to 3 years for it to become 1 cm in size (~0.25 cm per year)
  - Thus, the rate of growth of adenoma is slow (~0.25 cm per year, before becoming a worrisome size of < 1 cm, and once the polyp is 1 cm in size, the cumulative risk of the development of CRC is about 1% per year.

- Overall, annual conversion rate of 0.25
- Adenomas
  - Annual rate of conversion, 3%
  - > 1 cm, 3%
  - Villous components, 17%
  - Severe dysplasia, 37%
- Mean doubling time of CRC, ~ 620 days
- Prior to resection for CRC, perform staging diagnostic imaging so that IOUS (intraoperative ultrasonography) does not need to be performed.
- "in patients whose tumor [CRC] recurs after hepatic resection, the liver is the initial site of recurrence in about 35% (Feldman M., et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. Saunders/Elsevier, Philadelphia, 2010, page 2232).
- Risk of postoperative relapse of CRC
  Stage II, 20% to 30%
  Stage III, 50% to 80%
- Surveillance must be continued.
- Patients with small rectal hyperplastic polyps should be considered to have normal colonoscopies, and therefore the interval before the subsequent colonoscopy should be 10 years. An exception is patients with a hyperplastic polyposis syndrome. They are at increased risk for adenomas and colorectal cancer and need to be identified for more intensive follow up.
- Persons with one or two small tubular adenomas (<1cm) , and with only low grade dysplasia should have their next follow up colonoscopy in 5 to 10 years. The precise timing within this interval should be based on other clinical factors (such as prior colonoscopy findings, family history, and the preferences of the patient and judgment of the physician).
- Patients with 3 to 10 adenomas, or any adenoma 1 cm, or any adenoma with villous features, or high grade dysplasia should have their next follow up colonoscopy in 3 years
- If the follow up colonoscopy is normal or shows only one or two small tubular adenomas with low-grade dysplasia, then the interval for the subsequent examination should be 5 years.

- Persons who have more than 10 adenomas at one examination should be examined at a shorter (<3 years) interval established by clinical judgment, and the clinician should consider the possibility of an underlying familial syndrome.
- Persons with sessile adenomas that are removed piecemeal should be considered for follow up at short intervals (2 to 6 months) to verify complete removal.
- Once complete removal has been established, subsequent surveillance needs to be individualized based on the endoscopist's judgment.
- More intensive surveillance is indicated when the family history may indicate hereditary nonpolyposis colorectal cancer.
- Every 5-10 years, except every 3 years for multiple, large, villous and proximal initial lesions.
- Number- for each additional adenoma, OR=1.32
- Size- for each additional 10 mm adenoma size, OR=1.56
- Villous – OR=1.40
- Proximal – OR=1.68

Source: Winawer, Sidney J. Screening and surveillance for colorectal cancer: review and rationale. *2009 ACG Annual Postgraduate Course:*21- 25.

Index colonoscopy shows adenomatous polyp (s), which are removed.

- Give the approximate 10 yr rate of recurrent adenomatous polyp or of colorectal cancer (CRC).
    - The recurrence rates of adenomatous polyps or CRC are dependent on the number of index polyps, and the duration of follow up

# of adenomas removed at index colonoscopy	Types of recurrent lesion	Approximate recurrence rate at 10 yrs
1	Polyps	30%
> 1		70%
1	CRC	2%
> 1		10%

- In addition to the number of polyps and duration of follow-up, other features increase the cumulative risk of recurrence include:
  - Size
    - ≥ 1 cm in size
  - Histopathology
    - Villous
    - Severe dysplasia
  - Age of patient
    - Older

- Give the features of a malignant colonic polyp which suggest a favourable prognosis.
  - Differentiation margin
    - Well or moderately clear
    - > 2 mm margin
  - Invasion
    - Submucosa No
    - Veins No
    - Lymphatics No

Adapted from Feldman M., et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. Saunders/Elsevier, Philadelphia, 2010, Table 122.10, page 2170.

- Give 3 additional risk factors (ARF) which more than double usual risk of polyp recurrence.
  - The risk of AAP recurrence depends on duration of follow up and the presence of three additional risk factors (ARF):
    - ≥ 3 index adenomas
    - > 60 years of age
    - a parent with CRC

  - The approximate **polyp recurrence rates** are:

Time (years) after index polypectomy	AAP	ARF
3	4%	10%
6	8%	20%

Useful background:

- The guidelines for CRC screening and surveillance are frequently being updated (U.S. Preventive Services Task Force. *Ann Int* Med 2008:627-37.; Rex DK, et al. *Am J Gastroenterol* 2009:739-50.)
- Even with following guidelines, CRC may develop in the interval between polypectomies.
  - These "interval cancers" develop in about 0.6% of persons screened, having polypectomy, and then followed with an appropriate surveillance program (Winawer SJ, et al. *CA Cancer J Clin* 2006:143-59.; Rex DK, et al. *Gastroenterology* 2006: 1865-71).
- Colonoscopy screening provides its greatest benefit from the detection of left-sided lesions. In fact, the usefulness of colonoscopy to reduce the risk of right-sided CRC has been challenged.
- Newer endoscopy equipment such as high-definition, narrow band imaging, or chromoendoscopy (including FICS [fujinon intelligent chromoendoscopy system], and the Pentax-scan) have yet to be shown to constantly improve polyp detection and CRC mortality
- Persons with CRC associated with K-ras mutations do not respond as well to anti-ECFR therapy (Jiang Y, et al. *Cancer* 2009)

Abbreviations: EGFR, epidermal growth factor receptor; FICS, fujinon intelligent chromoendoscopy system; FIT, fecal immunochemical test

Guidelines for screening and surveillance for the early detection of colorectal adenomas and cancer in individuals at increased risk or at high risk

Risk category	Age to begin	Recommendation	Comment
Increased risk – patients with history of polyps at prior colonoscopy			
➢ Patients with small rectal hyperplastic polyps	-	- Colonoscopy or other screening options at intervals recommended for average-risk individuals	▪ An exception is made for patients with – A hyperplastic polyposis syndrome – > 1 cm – Multiple above rectosigmoid – Serrated ▪ They are then at increased risk for adenomas and colorectal cancer and need to be identified for more intensive follow-up

Risk category	Age to begin	Recommendation	Comment
➢ Patients with 1 or 2 small tubular adenomas with low-grade dysplasia	○ 5 to 10 years after the initial polypectomy	– Colonoscopy	▪ The precise timing within this interval should be based on other clinical factors (such as prior colonoscopy findings, family history, and the preferences of the patient and judgment of the physician)
➢ Patients with 3 to 10 adenomas, or 1 adenoma > 1 cm, or any adenoma with villous features or high-grade dysplasia	○ 3 years after the initial polypectomy	– Colonoscopy	▪ Adenomas must have been completely removed. If the follow-up colonoscopy is normal or shows only 1 or 2 small tubular adenomas with low-grade dysplasia, then the interval for the subsequent examination should be 5 years.
➢ Patients with > 10 adenomas on a single examination	○ < 3 years after the initial polypectomy	– Colonoscopy	▪ Consider the possibility of an underlying familial syndrome.
➢ Patients with sessile adenomas that are removed piecemeal	○ 2 to 6 months to verify complete removal	– Colonoscopy	▪ Once complete removal has been established subsequent surveillance needs to be individualized based on the endoscopist's judgment. Completeness of removal should be based on both endoscopic and pathologic assessments.
Increased risk – patients with colorectal cancer (CRC)			
➢ Patient undergoing curative resection for colon or rectal cancer		– Colonoscopy	▪ This colonoscopy at 1 year is in addition to perioperative colonoscopy for synchronous tumours. ▪ If examination performed at 1 year is normal, then interval before next subsequent examination should be 3 years. ▪ If that colonoscopy is normal, then interval before next subsequent examination should be 5 years. Following examination at 1 year, the intervals before subsequent examinations may be shortened if there is evidence of HNPCC or if adenoma findings warrant earlier colonoscopy.

Risk category	Age to begin	Recommendation	Comment
➢ Patients with colon and rectal cancer should undergo high-quality perioperative colonoscopy to ensure there is no synchronous CRC	○ 3 to 6 months after cancer resection, if no unresectable metastases found during surgery: alternatively, colonoscopy 1 year after resection, or 1 year following performance of colonoscopy performed to clear colon of synchronous disease	– Colonoscopy	▪ In the case of nonobstructing tumours, this can be done by preoperative colonoscopy. ▪ In the case of obstructing colon cancers, CTC with intravenous contrast or DCBE can be used to detect synchronous neoplasms in the proximal colon.
Increase risk- patients with a family history			
➢ Either colorectal cancer or adenomatous polyps in a first-degree relative before age 60 years or in 2 or more first-degree relatives at any age	○ Age 40 years, or 10 years before the youngest case in the immediate family	– Colonoscopy	▪ Every 5 years
➢ Either colorectal cancer or adenomatous polyps in a first – degree relative age 60 or older or in 2 second – degree relatives with colorectal cancer	○ Age 40 years	– Screening options at intervals recommended for average – risk individuals	▪ Screening should be at an earlier age, but individuals may choose to be screened with any recommended form of testing
High risk			
➢ Genetic diagnosis of FAP or suspected FAP without genetic testing evidence	○ Age 10 to 12 years	– Annual FSIG to determine if the individual is expressing the genetic abnormality and counseling to consider genetic testing	▪ If the genetic test is positive, colectomy should be considered

Risk category	Age to begin	Recommendation	Comment
➢ Genetic or clinical diagnosis of HNPCC or individual at increased risk of HNPCC	○ Age 20 to 25 years, or 10 years before the youngest case in the immediate family	– Colonoscopy every 1 to 2 years and counseling to consider genetic testing	▪ Genetic testing for HNPCC should be offered to first-degree relatives of persons with a known inherited MMR gene mutation. It should also be offered when the family mutation is not already known, but 1 of the first 3 of the modified Bethesda criteria is present.
➢ Inflammatory bowel disease, chronic ulcerative colitis and Crohn colitis	○ Cancer risk begins to be significant 8 years after the onset of pancolitis or 12 to 15 years after the onset of left-sided colitis (UC or CC)	– Colonoscopy with biopsies for dysplasia	▪ Every 1 to 2 years ▪ These patients are best referred to a center with experience in the surveillance and management of inflammatory bowel disease

Abbreviations: CC, Crohn colitis; CRC, colorectal cancer; CTC, computed tomographic colography; DCBE, double-contrast barium enema; FAP, familial adenomatous polyposis; FSIG, flexible sigmoidoscopy; HNPCC, hereditary nonpolyposis colon cancer (Lynch syndrome); MMR, mismatch repair; UC, ulcerative colitis.

Printed with permission: Levin B, et al. *Gastroenterology* 2008;134(5): pg. 1588.

Pathology Alert

- "Pseudoadenomatous epithelium"
  - Ectopic benign epithelium below the muscularis mucosae (MM) may look like cancer (pseudoadenomatous epithelium), and has to be distinguished from invasion of mucosal adenocarcinoma through the MM.

- Give the recommended age of onset (years) and interval (every x years) for CRC screening for each of the following.

Group	Age	Interval
➢ Average risk	50	10
➢ Family history:		
○ one first-degree relative (parent, sibling or child) with a CRC or AP (adenomatous colonic polyp) at age < 60 or 10 yr younger than the earliest diagnosis in family	40	5
○ one first-degree relative (parent, sibling or child) with a CRC or AP (adenomatous colonic polyp) at age > 60	40	10
○ two first-degree relatives with CRC at any age	40	5
○ two second-degree relatives (grandparents, aunt/uncle) with CRC at any age	40	10
○ one second degree or third-degree relative (great-grandparent or cousin) with CRC at any age	40	10
○ Syndromic familial risk:		
familial adenomatous polyposis (FAP): genetic diagnosis, or clinical diagnosis from family history	10	1-2
○ HNPCC: genetic diagnosis, or clinical diagnosis from family history	20, or 10 yr earlier than youngest age of CRC in the family	1-2

Source: *World Gastroenterology Organization and International Digestive Cancer Alliance, chaired by Professor S. Winawek, USA*.

Useful Reading for Intestinal Polyposis Syndromes

Please see Feldman M., et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. Saunders/Elsevier, Philadelphia, 2010,

Table 122.13, page 2177, "Classification of Gastrointestinal Polyposis Syndromes"

Table 122.14, page 2177, "Adenomatosis Polyposis Syndromes"

Table 122.12, page 2178, "Schematic Diagram of the APC gene, its mutations and Functional Domains of the Protein"

Table 122.15, "Cancer Risks and Screening Recommendations in the Hereditary Polyposis Syndromes"

Table 122.17, page 2185, "Familial Hamartomatous Polyposis Syndromes"

- Give 5 inherited colon cancer syndromes, and for each give the affected gene (s), and the demonstrated mutation frequency (%) in the index case, and the likelihood (%) of finding a mutation in the index case.

Syndrome	Gene(s)	Demonstrated mutation frequency (%) Index Case
○ Adenomas		
- FAP, AFAP	-APC gene pathway mutations in B-catenin and AXIN, attenuated APC (dominant)	90
- MAP	-MYH (recessive)	100
- HNPCC	-MLH1, MSH2, MSH6	50-70
○ Hamartomas		
- Peutz-Jegher syndrome (PJS)	-Germline mutation of serine/threonidine kinase gene (STK11) or chromosome 19	50
- Juvenile polyposis syndrome	-SMAD4 on chromosome 8; BMPR1A,on chromosome 10	50
- Cowden syndrome	-PTEN	90

Abbreviations: FAP, familial adenomatous polyposis; AFAP, attenuated familial adenomatous polyposis; MAP, modified adenomatous polyposis; HNPCC, hereditary non-polyposis colon cancer (Lynch syndrome)

Source: World Gastroenterology Organization and International Digestive Cancer Alliance, chaired by Professor S. Winawek, USA.

FAP is due to APC gene pathway mutations in B-catenin and Axin

- Give the names, genetic mutations, and recommended frequency of surveillance colonoscopy in two FAP attenuated syndromes, AFAP and MUTYH (MYH gene).

  - AFAP (attenuated form of FAP)
    - < 100 adenomas, often in proximal colon
    - Some duodenal and gastric polyp associations as classic FAP
    - Loss of the 5' and 3' regions of FAP
    - CRC develops later than in FAP, ~5 years rather than 32 years
    - Surveillance colonoscopy of 2 year
  - MUTYH (aka MYH) gene (MAP)
    - 15-100 colonic adenomas
    - Defective MUTYH gene causes G:C → T:A translocation
    - Autosomal recessive
    - ↑ risk of CRC with biallelic MUTYH mutations
    - Colonoscopic screening age 18 to 20 with surveillance of 2 years

- Give a classification of **multiple colonic polyps** (polyposis).
  - Inherited
    - Adenomas
      - FAP (familial adenomatosis)
      - Variants of FAP
      - Gardner
      - Turcot
      - AFAP (attenuated FAP)
      - MUTYH
      - Bloom syndrome
      - Familial tooth agenesis syndrome
      - Hamartomas
      - PJS (Peutz-Jegher Syndrome)
      - JPS (Juvenile polyposis syndrome)
      - PTEN hamartomas
        - Cowden disease (CS)
        - BRR (Bannayan-Ruvalcaba-Riley) syndrome
      - Neurofibromatosis and ganglioneuromatosis
      - Tuberous sclerosis (TS)

MCQ ALERT

HNPCC-Lynch syndrome is inherited but **not** a polyposis syndrome

- Non-inherited
  - Inflammatory (pseudopolyps)
  - Cap polyposis
  - HPS (hyperplastic polyposis syndrome)
    - ≥ 5 hyperplastic polyps proximal to sigmoid colon, 2 of which are 10 mm; or
  - Lymphomatous polyposis
    - Hodgkin and NHL (non-Hodgkin lymphoma)
    - MZL (mantle zone lymphoma)
  - NLH (nodular lymphoid hyperplasia)
    - May be associated with Gardner syndrome
  - Cronkite-Canada syndrome (CSS)

ADENOMATOUS POLYPOSIS SYNDROMES

Prevalence $20/10^5$,and
Penetrance, 80%

Familial Adenomatous Polyposis (FAP)

- Genetics

Gene mutation	Chromosome
APC - Truncated germline mutation (stop codon) of first allele from affected parent causes APC mutation in all cells in the body - Loss of normal phosphorylation of B-catenin, with loss of inactivation of B-catenin, leading to instability of chromosomes, and their segregation - There may also be germline mutations of axin - Unaffected parent passes on somatic mutations in the mutations in the mutation cluster region near the centre of all APC gene or lost second allele	5q21-q22 region

- Genetic testing in FAP is important because there may be skipped generations, and 20% of FAP patients may have a mutation.
- It is important in the screening of the family to know the genetic mutation in the index patient (performed on DNA from peripheral blood WBCs), and to better focus on which mutation to look for in the next-of-kin, and to provide better genetic counseling.

- While all the family needs to be tested, if resources are a limiting factor, give the family groups that should be tested in FAP and MUTYH.
  - FAP autosomal dominant (1 in 2)
    - Parents and children
  - MUTYH autosomal recessive (1 in 4)
    - Siblings and spouses

Useful background reminders

- MYH is a base-excision-repair gene on chromosome 1

➢ Types

- Classic FAP and its variants
  - Gardner syndrome
  - Turcot syndrome
  - Attenuated FAP (AFAP)
- Synchronous CRCs occur in about half of FAP patients.
- Even with recommended colonoscopic screening and surveillance, about a quarter already have CRC (perhaps time of recommended colectomy needs to be moved earlier).

Exam Alert

- What if the clinical examiner tells you that the patient has colonic polyps and hands you a fundoscope.
- She/he is expecting you to look for pigmented lesions in the ocular fundus, suggesting CHRPE in the Gardner variant of FAP.

➢ Pathophysiology

- Give 4 biochemical changes that occur during the development of CRC.

- ↑ CEA (carcinoembryonic antigen)
- ↑ matrix metalloproteinases
  - MMP-1
  - MT1 – MMP
- ↑ EGF (vascular endothelial growth factors) increase angiogenesis and vasculization
- ↑ selectins (on endothelium)
- ↑ sialoglycoproteins (on tumor)

➢ Clinical

- Give 10 extracolonic manifestations of colorectal cancer (CRC) syndromes.

➢ Remember

  - FAP in its classical form may be associated with dental abnormalities and osteomas of the jaw, without being considered to be a Gardner variant.
  - FAP + CNS tumor (medulloblastoma) = Turcot syndrome
  - MUTHY
    - Also remember, osteomas and CHRPH may occur in MUTYH

➢ FAP

  - Duodenum
    - Ampullary cancer
    - Duodenal cancer
    - ↑ risk of epithelial dysplasia is associated with
      - ↑ size
      - Site-associated duodenal polyposis
      - Association – Non-H.pylori antral gastritis
  - Duodenal FAP polyps
    - Occur in 60% to 90% FAP patients
    - Usually periampullary region, and > half involve the ampulla of Vater
    - ~10% lifetime risk of duodenal cancer

- Give the role of APC gene function, nuclear β-catenin, the Wat signal pathway, the LEF (lymphoid enhancer factor) / TCF (T-cell factor) family in the development of CRC.

➢ Normal

  - APC (tumor suppressor) gene
    - Association with E-cadherin → cell-cell adhesion
    - Binds β-catenin → ↑ phosphorylation
    - ↓ β-catenin - ↓ stimulation of Wnt-Tcf signal pathway
      - ↓ proliferation
      - ↑ apoptosis

- APC gene mutation
  - ↓ cell-cell adhesion
  - ↓ β-catenin phosphorylation
    - ↑ unphosphorylated β catenin complex with LEF / TCF
    - ↑ Wnt-Tcf
  - Target genes
    - ↑ proliferation
    - ↓ apoptosis

- Genetic testing is part of the standard management of families with FAP.

- Give three methods used for genetic testing in FAP to confirm the diagnosis of FAP in suspected cases, and to determine if a person from a family with FAP is a gene carrier?
  - *In vitro* protein truncation in FAP
    - Detects the presence of truncating mutations in vitro
    - Detects a mutation in 80% to 90% of affected families known to have FAP
    - Near 100% effective in family members once the presence of a mutation has been found in an affected person
  - Gene sequencing
    - Often preceded by single-strand conformational polymorphism (SSCP) or denaturing gradient gel electrophoresis (DGGE) to narrow the area of the gene where sequencing is to be performed
    - Up to 95% effective in finding a disease-causing mutation if it is present
    - Near 100% effective in family members once the presence of a mutation has been found in an affected person
  - Linkage testing
    - Used if other methods unsuccessful
    - Two or more affected persons from two generations must be living for DNA to be obtained
    - Effective in >95% of families, with >98% accuracy with present linkage marker

- Genotype-phenotype correlations:
  - These have not yet been found to be of precise use in the clinical setting
  - The following correlations have been made:
    - CHRPE (congenital hypertrophy of the retinal pigment epithelium): present in families with mutations distal to exon 9 of the APC gene
    - Dense polyposis: present with mutations in the mid portion of exon 15
    - AFAP/AAPC: found with mutation in the extreme proximal or distal end of the gene
    - Osteomas and desmoids (Gardner's syndrome): more commonly found with mutations in the distal portion of exon 15

Abbreviations: CHRPE, congenital hypertrophy of the retinal pigment epithelium; DGGE, denaturing gradient gel electrophoresis; SSCP, single-strand conformational polymorphism

Adapted from: Doxey BW, et al. *Clin Gastroenterol Hepatol*. 2005;3(7):633-41; and Burt R, Neklason DW. *Gastroenterology* 2005;128(6):1696-716.

- Stomach
  - Fundic gland polyps
- A polyp in the fundic area of the stomach is a polyp in the fundus, and should not be called a fundic gland until the histopathology of the lesion proves this diagnosis.
- In FAP, when polyps are seen in the fundic area of the stomach
  - < 5% are adenomas
  - 95% are fundic gland polyps (FGP) however at least a quarter of these FGPs already have epithelial dysplasia
- Small bowel FAP polyps
  - Jejunum, 40%
  - Ileum, 20%
  - Distinguished from lymphoid hyperplasia
  - Low risk of malignancy

- Gardner syndrome (associated with FAP)
  - Eye
    - CHRPE (congenital hypertrophy of the retinal pigmented epithelium)
      - Multiple in 63%
      - Bilateral in 87%
  - Teeth
    - Supernumerary teeth
    - Familial tooth agenesis
      - Caused by mutation in APC pathway (AXIN2)
      - Both adenomatous and hyperplastic colonic polyps
  - Skin (benign soft tissue tumors)
    - Desmoid
    - Fibromas
    - Lipomas
    - Epidermoid (aka inclusion cysts)
    - Sebaceous cysts
    - Diffuse mesenteric fibromatosis
      - $00/10^5$ person-years
      - Treat with NSAIDs and tamoxifin chemotherapy, colectomy small bowel transplantation
      - May be a lethal association
      - Mesentery
  - Bone
    - Osteomas
      - Skull
      - Jaw
      - Long bones
- Non-CNS tumors
  - Hepatoblastoma
  - Thyroid papillary tumor
  - Adrenal tumor
- Turcot syndrome (associated with FAP)
  - Medulloblastoma
  - Cerebellar

SO YOU WANT TO BE A GASTROENTEROLOGIST

- The second most lethal complication of the Gardner variant of FAP is desmoid tumor (diffuse mesenteric fibromatosis).
- A strong family history of FAP increases the risk of having desmoid tumors.
- Treatment may include an NSAID, tamoxifen, sulindac plus tamoxifen, progesterone; chemotherapy; resection, and even small bowel transplantation.

- Give the **Church** et al. staging system for desmoid tumors in the Gardner variant of FAP.
  - Staging system for desmoid tumors in Gardner variant of FAP

Findings	I	II	III	IV
- Symptoms	No	Mild	Moderate*	Severe
- Size, cm	< 10	< 10	10-20	> 20
- Growth	No	No	Slow	Rapid

*May be associated with symptoms of obstruction of the bowel or ureter

Adapted from: Feldman M., et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. Saunders/Elsevier, Philadelphia, 2010, page 2182.

Cute Quotes

"The presence of multiple [CHRPE] lesions appears to be a reliable marker for gene carriage in FAP" (Feldman M., et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. Saunders/Elsevier, Philadelphia, 2010, page 2180).

TURCOT SYNDROME

- Definition: "…. a syndrome of familial colonic polyposis with primary tumors of the central nervous system" (Feldman M., et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. Saunders/Elsevier, Philadelphia, 2010, page 2184).

SO YOU WANT TO BE A GASTROENTEROLOGIST!

- The Turcot syndrome is considered to be variant of FAP, and as such has a mutation in the APC gene.

- Give the reason why the Turcot syndrome may be misclassified, and should be considered either as a variant of HNPCC, or an overlap of both FAP and HNPCC.
  - In the Turcot syndrome, the gene mutations are in FAP, or in DNA MMR, the same germline mutation seen in HNPCC.

- Give the difference in the CNS presentation of Turcot syndrome, depending upon which germline mutation is present.
  - Gene mutation in
    - APC
      - Medulloblastomas
    - DNA MMR
      - Glioblastoma multiforme tumors (familial tooth agenesis)
  - It may be surprising to learn, but there are actually at least two attenuated adenomatous polyposis syndrome.

- Give the median age of onset of CRC in the 4 phenotypes of FAP.

Phenotype	Age, yrs
Profuse	39
Intermediate	39-50
Attenuated (AFAP)	>50 (R colon)
MYH (MAP)	>60 (recessive)

- Give the clinical management of FAP (familial adenomatous polyposis).

➢ Genetic testing

- Consider genetic testing between ages 10 to 12 years, as it will first be clinically useful.
- May need to begin in first decade of life to determine who should be screened for hepatoblastoma

➢ GI tract screening

- Colon cancer risk > 90%
- Sigmoidoscopy in gene carriers q 1 to 2 years, beginning at age 10 years, or in all at-risk persons if genetic testing is not done or not informative.
- Colonoscopy q 2 years beginning at age 20 in families with AFAP/AAPC, or sometimes earlier, depending on the age of polyp emergence in other family members
- Upper GI endoscopy
  - Upper GI tract (5-10% cancer risk for duodenal or peri-ampillary, 0.5% for gastric)
  - Begin when colon polyps emerge or by age 25 years
  - Repeat q 1 to 3 years, depending on the number of polyps, their size and histology
  - Side viewing should be performed as part of the examination to carefully identify and examine the duodenal papilla.

- Duodenum
  - About 60% to 90% of FAP patients have periampullary adenomatous polyps, and about 10% will develop duodenal cancer.
  - Clearly, FAP patients require surveillance with SV-EGD (side-viewing EGD, esophagogastroduodenoscopy).
  - Risk stratification for the development of duodenal cancer is based on the Spigelman classification.
  - This Spigelman classification provides guidance for EGD surveillance of these duodenal adenomas. Until EUS has refined our appreciation for any change in the currently recommended EGD surveillance guidelines, this remains the standard of care.
  - Screening with SV-EGD should begin at 2 years of age, and then be followed by regular SV-EGD surveillance.

- Give the recommended interval of duodenoscopic screening (visualization and biopsy) of duodenal polyps in FAP, using the **Spigelman staging criteria**.

Score	1	2	3
○ Polyp count	1-4	5-20	>20
○ Polyp size (mm)	1-4	5-10	>10
○ Histologic type	Tubular	Tubulovillous	Villous
○ Grade of intraepithelial neoplasia	Low-grade	Intermediate*	High-grade

Grade	Surveillance interval (years)
0	5
I, II	3
III	1
IV	3-6 months, or pylorus preserving, duodenectomy, or Whipple procedure

Stage 0: 0 points, Stage I: 1-4 points, Stage II: 5-6 points, Stage III: 7-8 points, and stage IV: 9-12 points

*Intermediate grade is not existent in actualized classifications of intraepithelial neoplasia

Printed with permission: Schulmann K, et al. *Best Pract Res Clin Gastroenterol* 2007; 21(3): pg. 413.

  - Jejunum / Ileum
    - Diagnostic imaging should be done before colectomy.
    - Should be done if numerous or large adenomas are present in the duodenum
    - Frequency determined by number and size of lesions found
  - Pancreas (2% cancer risk) -periodic US (abdominal ultrasound) after age 20
  - Hepatoblastoma (1.6 % of children <5 yrs) EUS (endoscopic ultrasound), AFP (alpha-fetoprotein) during first decade of life

- Non GI tract screening
  - thyroid (2%) – annual thyroid exam starting age 20
  - cerebellar meduloblastoma (<1%) – possible periodic head CT

Adapted from: Half EE, and Bresalier RS. *Curr Opin Gastroenterol* 2004;20(1):32-42.

- Give the recommended method, age to begin, interval of screening, and management of the person with FAP.

Screening method	Age to begin	Interval	Management
➢ Colonoscopy or flexible sigmoidoscopy	○ 10-12 years, or late teens if attenuated FAP	- If polyps are detected, screen annually until colectomy	▪ Colectomy - When polyps too numerous to monitor safely - If polyps are ≥1 cm - Exhibit advanced histology - Removal of the rectum should be based on polyp burden and family history
➢ Flexible sigmoidoscopy	○ Within two years after colectomy	- Every 6 months to 3 years depending on polyp size and number	▪ Chemoprevention with NSAIDs may be considered
➢ EGD with end and side viewing instrument	○ 20-25 years or at the onset of colonic polyps	- 3 yrs if stage[1] 0, II - 2 yrs if stage[1] III - 6-12 months if stage[1] 4	▪ Chemoprevention with NSAIDs is less effective for upper GI adenomas
➢ Physical examination	○ 10 to 12 years	- Annually	
➢ Physical exam, hepatic ultrasound, and alphafetoprotein	○ 6 months	- Every 6 months during first decade of life	
➢ Determined by location of suspected desmoids, often abdominal CT	○ When palpable mass or relevant symptoms present		

[1]Spigelman staging criteria

Printed with permission: Burt RW. *2007 AGA Institute Postgraduate Course.* pg 236.

- Improvement in survival from CRC
  10 yr global benefit LC > RC
  - Split dosing of preparation for colonoscopy is best prep'
  - If you find a prox-polyp-look again, because of likely additional missed lesion
  - I serrated adenoma = risk of 3 adenomas
  - "ADR" – adenoma detection rate
  - ADR for second colonoscopy = 9.8% = pick – up for retroflexed view in cecum
  - ADR correlates well with RC serrated lesion detection

- "FDAs" (Flat & depressed adenomas)
  - Height < ½ of diameter
  - Aggressive biological behaviour
    - ↓ K Ras and ADC mutations
    - Alternate neoplastic pathways
  - More advanced SX ↑ pathology

- Watch for LST – lateral spreading tumour

HYPERPLASTIC POLYPS

Serrated Polyps ("boot- / bell-shaped distorted crypts)

A single hyperplastic polyp normally does not have a malignant potential.

- Give three features of hyperplastic polyps which ↑ risk of malignant potential and provide the rationale for surveillance.
  - > 1 cm size
  - Multiple hyperplastic polyps
  - Serrated

- TSA
  - Shape
    - Often protuberant
  - Frequency
    - Infrequent
  - Site
    - Distal colon
  - Mutations
    - BRAF mutation
    - CpG island methylator phenotype
    - Microsatellite instability
  - Malignant potential is "significant"
    - LC Hyperplastic polyp (HP)
    - LC Traditional serrated adenoma (TSA)
    - RC Sessile serrated adenoma (SSA)
- SSA
  - Sessile or flat (subtle)
  - Proximal
    - More frequent

Serrated = distortion of crypts "boot-/bell-shaped"
Abbreviation: LC, left colon; RC, right colon

Note: Sessile serrated adenomas and serrated sessile hyperplastic polyps (SSH) may have malignant potential, and surveillance should be performed for these.

- Give the surveillance recommendations after resection of serrated polyps.

Resected polyp	Recommended surveillance interval
○ Typical single hyperplastic polyp	No surveillance recommended, unless: > 1 cm, multiple, large and proximally located
○ Sessile serrated adenoma (SSAs) (non dysplastic)	q 5 years if < 3 lesions, all < 1 cm size; q 3 years if ≥ 3 lesions, or any ≥ 1 cm size
○ Sessile serrated adenoma with dysplasia (SSAD)	q 3 years after ensuring complete resection
○ Traditional serrated adenoma	
○ Suspected type I hyperplastic polyposis (serrated adenomatous polyposis)	1-3 years, with resection of polyps > 5 mm

Printed with permission: Huang C.S. Am J Gastroenterol 2011;106:229-240.

Serrated Polyposis Syndrome (aka Hyperplastic Polyposis)

- Definition
  - Serrated (hyperplastic) polyps proximal to sigmoid colon, of which ≥ 2 ≥ 10 mm)
- Colonoscopy
  - Flat or sessile
  - Mucus cap
  - Pale
  - Abnormal vascular pattern
  - Fuzzy edges

- Give the relative risk (RR) of 3 GI cancers associated with BRCA2 mutations.

Site	RR
GB cholangiocarcinoma	5.0
Pancreatic cancer	3.5
Gastric cancer	2.6

Source*:* The Cancer risks in BRCA2 mutation carriers. The Breast Cancer Linkage Consortium. *J Natl Cancer Inst.* 1999;91(15):1310.

Clinical Reminder

- Lynch syndrome is an inherited polyp disorder, like familial adenomatous polyposis (FAP), but Lynch syndrome is **not** a Hereditary Polyposis syndrome (that's why Lynch syndrome is also known as HNPCC, Hereditary non-polyposis colon cancer).

- Give 5 the screening and management guidelines for Lynch syndrome

Cancer	Screening	Age to start	Interval	Treatment
○ Colon	Colonoscopy	20-25 yrs (or 10 yrs before the earliest diagnosis in the family)	Every 1-2 years	Consider colectomy if cancer or advanced adenoma is found
○ Endometrial / Ovarian	Endometrial biopsy (for pre-menopausal women) and transvaginal ultrasound (preferably day 1-10 of cycle) for premenopausal women	30-35 yrs (or 5-10 yrs before the earliest diagnosis in the family)	Annually	Consider prophylactic TAH/BSO after childbearing
	CA125	30-35 yrs	Every 6-12 months	Consider oral contraceptives for premeno-pausal women
○ Stomach	EGD	30-35 yrs	Every 1-2 yrs	
○ CNS	MRI	Only if CNS	Every 1-2 yrs	
○ Urinary tract	Pelvic and abdominal US	symptoms 30-35 yrs	Annually	
	Urinalysis with cytology	30-35 yrs		
○ Biliary tract, gallbladder	Liver function tests Small bowel	30-35 yrs	Every 1-2 yrs	
○ Small bowel	enteroclysis	30-35 yrs	Every 1-2 yrs	

Abbreviations: TAN/BSO, total abdominal hysterectomy, bilateral salpingo-oophorectomy; CNS, central nervous system; EGD, esophagogastroduodenoscopy.

Printed with permission: Burt RW. *2007 AGA Institute Postgraduate Course.* pg. 240.

Hamartomatous Polyposis Syndromes

- Give syndromes causing hamartomatous polyps
    - PJ (Peutz Jegher Syndrome)
    - JP (Juvenile Polyposis)
    - TS (tuberous sclerosis)
    - CCS (Cronkhite-Canada Syndrome)

- Give the clinical features which would make you suspect Cronkhite Canada Syndrome (CCS).
    - Skin and hair changes
        - Alopecia
        - Dystrophic nails
    - Protein – losing enteropathy
    - No family history of similar condition (CCS is not inherited)
    - GI hamartomatous polyps
        - Colon
        - Small intestine
        - Stomach

"How can I know who I am,

Until I see what I do?

How can I know what I value,

Until I see where I walk?"

Karl Weick

COLORECTAL CANCER

➢ Pathophysiology

- Give the molecular pathways of tumor initiation and progression of CRC.

  - Tumor initiation
    - ↓ function of APC genes such as β-catenin or AXIN7 number
    - Germline plus somatic mutation in FAP; 2 acquired somatic mutations in APC in sporatic adenomas from loss of function of both APC alleles
  - Tumor progression
    - ↑ K-Ras oncogene
      - The larger the adenoma, the greater the number of adenomas positive for K-Ras (small, 9%, large, 58%)
    - DCC
      - Small tubular / tubulovillous adenoma, 12% with foci of cancer, 73%
    - p53
  - Stability genes
    - MMR (DNA mismatch repair) gene
      - Germline mutations
      - hMLH1
      - hMSH2
      - hMSH6
    - BER (base-excision repairs) gene
      - MUTYII (mutated BER gene; aka MYN)
      - MMR gene mutations load to MSI (microsatellite instability)
      - MSI in 15% sporatic and 55% of HNPCC CRC (colorectal cancers)

Abbreviation: DCC, deleted in colon cancer gene

➢ Risk Factors

- Give 15 factors which alter the risk for developing colonic adenomas or CRC.
  - Increased risk
    - Lifestyle
      - ↑ fat diet (especially red meat)
      - Obesity
      - Alcohol
      - Smoking (cigarettes)
      - Low calcium intake
    - Medical conditions
      - Ureterosigmoidostomy
        - Polyps (adenomas juvenile and hyperplastic) and CRC at stoma
        - Adenomas and CRC at stoma
      - Acromegaly: pooled odds ratio
        - Adenomas, 2.4
        - CRC, 4.3
      - Infection
        - Streptococcus bovis bacteremia,
        - JC virus
  - Decreased risk
    - Increasing dietary intake
      - Carbohydrate
      - Fibre
      - Calcium
      - Folate
      - Fresh fruit and vegetables
    - Physical exercise
    - Chemopreventive compounds
      - NSAIDs, ASA, Coxibs
      - Calcium, 20% ↓ risk of adenomas
      - Selenium, 20% ↓ risk of CRC
      - HRT (hormone replacement therapy)
      - UDCA (ursodeoxycholic acid)
  - Conversion rate (CR) to CRC
    - Adenoma, 30%
    - Villous, 17%
    - Dysplasia, 37%
    - Synchronous risk 5%
    - Metachronous risk 5%

Clinical Pearl

- Only Peutz-Jeghers syndrome is associated with ↑ risk of breast cancer (not through BRCA2 mutation)

- Give the pharmacological or nutritional agents which have been shown to be effective chemoprevention to reduce the risk of development or redevelopment of colorectal adenomas/CRCs.

  - Drugs
    - ASA
    - Coxibs
    - 5-ASA in IBD
    - Hormone replacement therapy (HRT) in post menopausal women
  - Nutrients
    - Selenium
    - Calcium (+ vitamin D)
    - Non-western diet (low intake of saturated fats in red meat)
    - High intake of green leafy vegetables
    - Possibly folate, vitamins C, E, B-carotene
    - Probably not dietary fiber
  - Exercise

Adapted from: Arber N, and Levin B. *Gastroenterology* 2008;134(4): 1224-1237; and Meyerhardt JA, et al. *JAMA* 2007;298(7): 754-764.

SO YOU WANT TO BE A GASTROENTEROLOGIST!

- Give the name of the gene in the APC gene family which increases the risk of colorectal cancer (CRC) in Ashkenazi Jewish persons, the gene which may be altered and increase the risk of CRC from the metabolism of nutrients and environmental agents.
  - In Ashkenazi Jewish persons
    - I 1307 K
  - Environmental risk
    - Methylene tetrahydrofolate reductase
    - N-acetyltransferase-1 and -2

SO YOU WANT TO BE A GASTROENTEROLOGIST!

- Give the postulated mechanism for the benefit of NSAIDs / ASA / Coxibs in the regressive of adenomatous polyps.
    - With adenomatous polyps → ↑ COX-2 expression
    - ↑ COX-2 → ↓ apoptosis
    - NSAIDs / ASA / Coxibs → ↓ COX-2
        - ↑ apoptosis
            - ↑ conversion of sphingomyelin to ceramide
        - ↑ arachidonic acid →
            - ↓ PPAR and gene
            - ↑ arachidonic acid

➢ Colonoscopy

- Narrowing band imaging (NBI) was introduced to overcome the limitations of white light endoscopy (WLE) for adenoma detection.
- There is difference in detection of polyps or adenomas with NBI and WLE.
- There is no difference in miss rates of polyps or adenomas with NBI and WLE.

Source: Pasha SF, et al. Am J Gastroenterol 2012; 107: 363-370.

➢ Use of EUS of rectum in CRC

- Sessile polyp
- Determine resectability of rectal CRC (surgeon needs 5 mm tumor-free margin)
- Miss rate of CRC on colonoscopy, ~10% (true figure unknown; appropriate figure to be quoted to patients: disputed)
- While the lifetime risk of CRC in pancolitis LS ↑ 10x, (pseudopolyps not an ↑ risk of CRC in UC)

➢ Treatment

- Adjuvant therapy
  - Adjuvant therapy within 8 weeks of resection for CRC
    - ↓ recurrence
    - ↑ survival
  - 5-FU (5-fluorouracil) plus levamisole (levamisole increases tumor response rates from 12% for 5-FU to 23% for 5-FU + levamisole

	Relative	Risk reduction
	CRC	Overall
	Recurrence	Mortality
➢ Dukes C / Stage III	42%	33%

  - 5-FU plus leucovorin > 5-FU plus levamisole in efficacy after curative surgery for CRC
  - 5-FU plus leucovorin plus oxaliplatin in Stage III
    - ↑ 3 year disease-free survival
    - May also be small benefit in Stage II
  - For rectal CRC Duke B2 / Stage II (transmural extension) or Duke C / Stage III (positive lymph nodes)

5-year rates	Radiation	Radiation plus chemotherapy
No recurrence	35	60
Survival	40	50

➢ Terminology: chemotherapy and / or radiotherapy for CRC given

- Before curative surgery – Neoadjuvant
- After curative surgery – Adjuvant
- There are studies in progress assessing preoperative (neoadjuvant) chemoradiotherapy, curative surgery, followed by 4 months of post-surgery (adjuvant) chemotherapy.
- The limitation to radiotherapy is its toxicity, but enhances of radiation therapy (e.g. capecitabine) may ↑ benefit without an ↑ toxicity
- Studies also examining possible benefit of infusion of 5-FU, leucovorin plus oxaliplatin (combination called FOLFOX).
- Adjuvant or neoadjuvant chemotherapy for Stage II or III resected CRC is often given as 5-FU plus leucovorin.

- Give the mechanism of action of 5-FUand leucovorin.
  - 5-FU – Binds to thymidylate synthetase → ↓ methylation of deoxyuridylic acid to thymidylic acid → ↓ DNA synthesis
  - Leucovorin – ↑ binding of 5-FU to thymidylate synthetase, thereby ↓ DNA synthesis (please see above)

Funding Alert: The Billion Dollar cost of reducing death from colon cancer by less that 1%

- Colorectal Cancer (CRC)
  - Lifetime risk of CRC 6%
  - Lifetime risk of dying from CRC
    - Screening surveillance
      - No 2.5%
      - Yes 1.6%
  - Annual CRC mortality
    - Risk reduction
      - Absolute ~ 0.9%
      - Relative ~36%

- Post-surgical colonoscopic follow-up
  - Colonoscopy 0→1→3→5 yr
  - CT yearly for 3 yr follow-up 0→1→3→5 yr
  - CEA q 3 months for 3 yr
  - Adjuvant chemotherapy with 5-FU can ↑ serum CEA (false elevation of CEA)

- Adjuvant chemo-radiotherapy
  - Benefit
    - Stage III MR 33%
    - Colon Ca recurrence 42% ↓
  - Use
    - T3/4 rectal cancer (locally advanced)
    - After resection of liver / lung metastases

- Surgery
  - TME, total mesenteric excision for CRC

- Surgical resection for liver metastases
  - 10% to 25% at presentation
  - Resection
    - < 5 metastases in liver
    - No extrahepatic metastases
    - No extensive liver involvement (< 70%)

- Non-operable, metastatic CRC
  - Chemotherapy
  - Stent
  - Photoabalation

DIVERSION COLITIS

- Definition: "…… an inflammatory process that occurs in segments of the colorectum that are diverted from the fecal stream by surgery.

- Clinical
  - May occur in persons with no pre-existing IBD
  - Few (6% to 30%) have symptoms, yet most have histopathological changes of colitis
  - Onset of symptoms is months to years after diversion

- Endoscopy
  - Severity of diversion colitis
    - Mild 52%
    - Moderate 44%
    - Severe 4%
  - Colitis in non-bypassed ("in continuity") colon 0%
    (Note: there are case reports of symptomatic UC developing in the "in continuity" colon in persons with established diversion colitis)

SO YOU WANT TO BE A GASTROENTEROLOGIST!

A patient with Crohn disease of the ileum undergoes a surgical diversion of the colon. Post-operatively, proctitis develops.

- Give features which favour the proctitis being recurrent Cohn disease (CD) versus diversion colitis (DC).

Features	CD	DC
○ Linear ulcers	+++	+
○ Transmural inflammation	+++	+
○ Architectural changes in crypts	+++	+
○ Epitheloid granulomas	+++	+
○ Lymphoid follicular hyperplasia	+	+

SO YOU WANT TO BE A GASTROENTEROLOGIST!

- ○ Diversion colitis (DC) may develop in the surgically diverted segment of colon. DC is speculated to be due to decrease in the diverted segment of obligate anaerobes and therefore in SCFAs (short-chain [length] fatty acids).
- ○ If possible, the continuity of the colon may be restored, with resolution of the colitis. In the event that the continuity of the bowel cannot or should not be restored, the deficiency of SCFAs and the impaired metabolism of the colonocytes can be restored by giving enemas of SCFAs.
- ○ Such SCFA enemas must be prepared by a pharmacist who is capable of compounding the preparation for the individual patient.

- Give the composition of the SCFA retention enemas. Alternatively, 5-ASA or steroid retention enemas may be useful.

Name of SCFA	mmol/L
○ Acetate	60
○ Proprionate	30
○ Butyrate	40

Mix in 22mmol/L NaCl, with an enema volumeof 60 mL, given bid per rectum (PR) or per mucous fistula.

- Pathology
  - Prominent lymphoid follicular hyperplasia in mucosa and submucosal
  - Aphthous ulcers (erosions over lymphoid follicles)
  - Diffuse neutrophil infiltrate
  - Crypts
    - Cryptitis
    - Crypt abscesses
  - If the diversion was for Crohn disease, granulomas may occur in the bypassed bowel.
  - May be difficult to distinguish from acute UC.

- Treatment

- Give the treatment of diversion colitis.

  - SCFA (short chain fatty acid) enemas
    - Prepared by "compounding" pharmacies, as sodium salts
      - Acetate 60 mmol
      - N-butyrate 40 mmol
      - Proprionate 30 mmol
      - Chloride (to achieve osmolality of 280 to 229 mOsm/L; 22 mmol
      - Hydroxide adjust pH to 7.0
  - 5-ASA enemas (minimal evidence)
    - Switch from, or add to SCFA enemas
  - Surgical reanastamosis
    - Especially early if patient has Crohn disease, to reduce likelihood of formation of stricture

RADIATION PROCTITIS

- Acute
  - Onset 6 weeks of radiation therapy
  - Usually stops after radiation treatment is completed
  - Symptoms may persist for 1 year after cessation of radiation therapy
  - In ~ 1/3 patients bleeding stops spontaneously within 6 months
  - Most often affects rectosigmoid portion of colon

- Chronic
  - Symptoms begin 9 months to 30 years after radiation therapy
  - Should be could “proctopathy” (chronic radiation proctopathy), since there is not an inflammation infiltration (no proctitis)
  - Fistula changes
  - May be associated with late (> 30 years) malignant transformation and CRC

- Pathology
  - Mucosa
    - Pale
    - Friable
    - Telangiectasias
  - Small or large abnormal areas
  - Obliterative end arterits
  - Chronic mucosal atrophy
  - Biopsy posterior and lateral walls of rectosigmoid to avoid area of maximum radiation exposure (uncertain if this ↓ risk of fistula formation)
  - Changes may be continuous or patchy (i.e. skip lesions)

- Treatment
  - SCFA (short chain fatty acid) enemas
  - Prepared by “compounding” pharmacies, as sodium salts
    - Acetate 60 mmol
    - N-butyrate 40 mmol
    - Proprionate 30 mmol
    - Chloride (to achieve osmolality of 280 to 229 mOsm/L; 22 mmol
    - Hydroxide adjust pH to 7.0
  - 5-ASA enemas (only case report evidence)
    - Switch from, or add to SCFA enemas
    - Amifostine is an organic thiophosphate which acts as a scavenger of free radicals, and which may be under study as a radioprotective agent of the GI tract and bladder.
  - Surgical reanastamosis
    - Especially early if patient has Crohn disease, to reduce likelihood of formation of stricture

- Give the treatment of radiation proctitis.
  - Pharmaceuticals
    - Constipation
      - Stool softeners, and other symptomatic measures
    - Obstruction (from strictures)
      - Endoscopic dilation for short and straight stricture
      - Try to avoid surgical resection (↑ risk of dehiscence)
    - Bleeding (from ectatic vessels)
      - Sucralfate enema, 2 g bid PR for 8 weeks (good response 4 weeks 77%; 8 weeks 92%)
      - Metronidazole 400 mg PO tid
    - Hormonal therapy
      - Estrogen +/- progesterone (evidence from only 1 case series)
    - Steroids, 5-ASA, SCFA enemas
      - No proven benefit
  - Endoscopic therapy
    - Formalin 4% to 5%, soaked gauze through sigmoidoscope, at 2 to 4 week intervals, for as long as required to stop bleeding
    - Cessation of bleeding
    - 2/3 require only 1 session

      1 month 60%
    - Bipolar (Bi) and Heater Probe (HP)
      - Reduction in severe bleeding over 1 year (vs control group [CG])

Bi	CG		HP	CG
75%	33%		67%	11%

TG therapeutic gain	Bi	42%
	HP	56%

  - Note that the apparent superior outcome with HP vs. Bi (56%, 42%) is largely due to the major difference in the control group, 11% vs. 33%, respectively.

- Hyperbaric O_2 (HO_2)

	HO_2	PL
Clinical response	89%	63%

For further details, please see the following:

- Clinical complications of chronic radiation enteritis or proctitis (Feldman M., et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. Saunders/Elsevier, Philadelphia, 2010, Table 39.1, page 644)
- Pathophysiological features of patients with late radiation enteropathy (Feldman M., et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. Saunders/Elsevier, Philadelphia, 2010, Table 39.2, page 645)
- Therapeutic options for patients with late radiation enteropathy (Feldman M., et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. Saunders/Elsevier, Philadelphia, 2010, Table 39.3, page 645)

MICROSCOPIC COLITIS

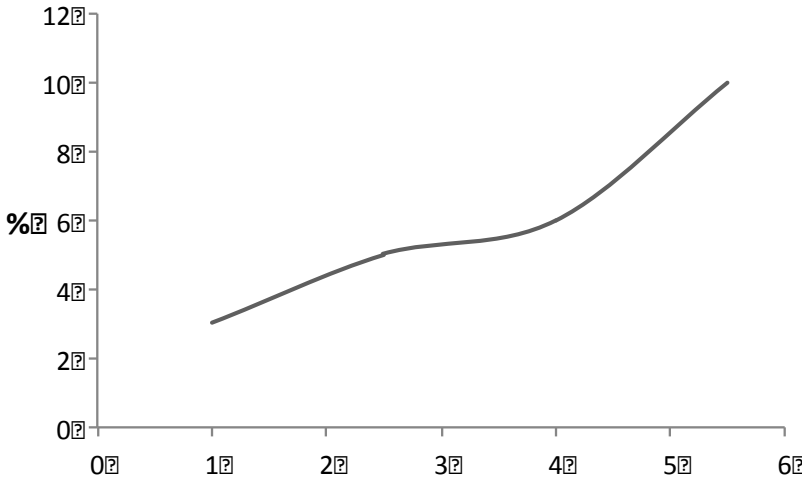
- Give 6 medications used for patients with microscopic colitis, and comment.
  - Loperamide (or other antidiarrheals)
  - Bismuth subsalicylate
  - Mesalamine
  - Cholestyramine
  - Budesonide
  - Prednisone
  - Azathioprine/6-mercaptopurine
  - Methotrexate

Source: Chande, N. *Can J Gastroenterol* 2008; 22: pg 687.

ISCHEMIC COLITIS

- Definition
  - "….. the condition that results when blood flow to the colon is reduced to a level insufficient to maintain [colonic] cellular metabolic function"

- Demography
  - Incidence 16 / 10^5
  - Women > men (women < 40 represent > 95% of cases of CI)
  - Mortality rate ~ 10%
  - Recurrence rates



- Anatomy
  - Blood supply of colon
    - SMA (superior mesenteric artery)
    - IMA (inferior mesenteric artery)
    - SHA (superior hemorrhoidal artery)

CLINICAL DI TIP

About 10% of persons > 60 have an asymptomatic occlusion of the IMA.

Site	Postulated usual cause	Linking of vessels	Name of water shed area
– Splenic flexure	Non-occlusive disease	L-branch of middle colic artery of SMA with ascending branch of left colic artery of IMA	Graffith point
– Sigmoid colon	Sigmoid colon	Final branch of sigmoid artery branch of IMA	IMA occlusion

➢ Risk factors (severe CI in ~ 5% of CI patients)

- Give the risk factors for colonic ischemia.

Risk factors		Odds ratio
CNS	- Cerebrovascular disease	3.20
CV	- PVD	7.9
	- Shock	4.32
	- ↑ BP	3.21
	- IHD / HF	2.6 – 4.75
	- AF	2.21
	- ↓ BP	1.85
Lung	- COPD	2.70-3.13
Blood	- Thrombophilia	
	- Sickle cell crisis	
Kidney	- CKD	8.50

Risk factors		Odds ratio
○ GI	- Any cancer	3.20
	- ↑ BM	2.36
	- IBS	2.01
	- Colon cancer	1.68
	- ↓ BM	1.62
○ Metabolic	- Dyslipidemia	2.13
	- Diabetes	1.82
○ MSK	- Systemic disorders	4.67
	- RA	3.27
○ Surgery	- Abdominal	18.4
	- Ileostomy	3.80
	- Aortic	3.58
	- Laparoscopy	2.90
○ Drugs		

Abbreviations: AF, atrial fibrillation; BM, bowel movement; CKD, chronic kidney disease; CNS, central nervous system; COPD, chronic obstructive disease; CRC, colorectal cancer; CV, cardiovascular; BP, blood pressure; HF, heart failure; IBS, irritable bowel syndrome; IHD, ischemic heart disease; MSK, musculoskeletal; OR, odds ratio; PVD, peripheral vascular disease; RA, rheumatoid arthritis

Adapted from: ACG Clinical Guideline, Brandt LJ, et al. Am J Gastroenterol 2015, Tables 110-18-44, page 22; Table 7, page 2.

- Drugs
  - The evidence is not strong for most of the drugs suggested to be associated with colonic ischemia

			↑ risk	Odds ratio
–	CNS	▪ Psychotropic		3.7
–	GI	▪ Constipation-associated drugs		
		– All drugs	0.68	
		– Opioids	1.96	
		– Non-opioids	1.75	
		– Warfarin	4.33	
		▪ Laxatives		4.73
		▪ Colitis, antibiotic associated		3.3
–	Metabolic	▪ Hormones (“female hormones”)		1.88

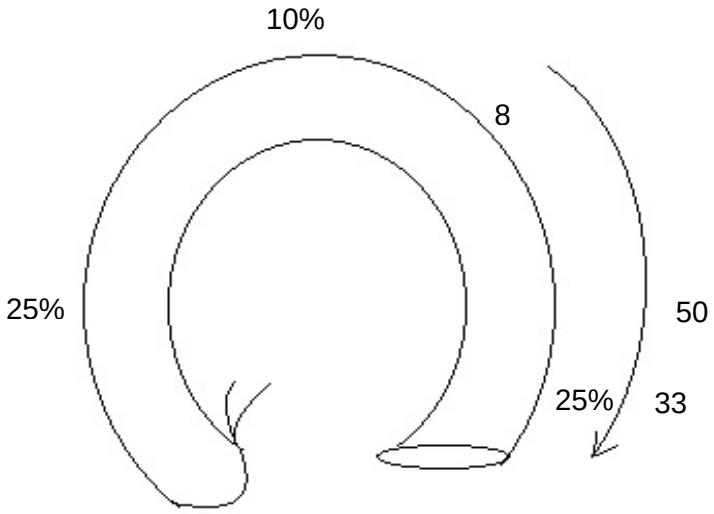
➢ Clinical

- Non-isolated R-colon ischemia
  - Sudden, central abdominal pain (milder that with AMI [acute mesenteric ischemia])
    - 78-87%
    - Sequence: pain – urgency – bloody diarrhea 50%
  - Diarrhea
    - Watery 19-56%
    - Bloody 35%
  - Urge to defecate
  - BRBPR (bright red / maroon-colored blood per rectum)
    - 58-84%
  - Pertained signs
  - Vomiting nausea 30%

- Isolated R-colon ischemia (IRCI)
  - More pain but less bleeding
  - When bleeding occurs
    - ↑ severity

➢ Pathology

- Gross
  - Site



Pancolonic 7%

  - Reversible changes
    - Subepithelial bleeding
    - Edema
    - Colitis
    - Ulceration
  - Irreversible changes
    - Hemorrhagic nodules
    - Early
      - Fulminant colitis (5%)
      - Stricture (14%)
      - Gangrene

    Late
      - Chronic ischemic colitis

- Pathognomic changes
  - Infarction (60%) plus
  - Ghost cells (in 20%)
- Non-specific changes
  - Bleeding
    - Mucosal
    - Submucosal
  - Edema
  - Inflammation
    - ↑ PMNs (↑ neutrophils)
- Fibrin thrombi

CLINICAL CAUTION

The mortality rate is higher for isolated, right-sided CI (IRCI)

- Laboratory
  - The diagnosis of CI must be suspected clinically
  - Laboratory tests are largely non-specific and non-sensitive
  - Blood
    - In the appropriate clinical setting, suspect severe CI with
      - ↓ Hg < 12 g/dL
      - ↓ Albumin < 2.8 g/L
      - ↓ pH (metabolic acidosis)
      - ↓ Na^{+}_{s} < 136 mEq/L
      - ↑ WBC > 15 cells / cm
      - ↑ LDH > 350 U/L
      - ↑ BUN > 20 mg/dL
  - Stool cultures
    - Because CI may be associated with
      - C. difficile infection
      - E. coli O57:H7

Abbreviations: BUN, blood urea nitrogen; Hg, hemoglobin; LDH, lactate dehydrogenase; Na^{+}_{s}, serum sodium concentration; WBC, white blood cells

- Diagnostic imaging
  - Abdominal film
    - Dilation of colon
    - Thick wall
    - Edema
    - "thumb printing" (pseudotumors)
    - Pneumatosis coli (circumferential intramural air)
    - Venous gas in portomesenteric system (36%)
  - CT with contrast
    - Superior performance characteristics for
      - Gangrene
      - Pneumatosis
    - Also
      - Ascites ~ 1/3
      - Target sign / halo sign ~ ¼
      - Fat stranding (100% in one study)
  - CTA (multiphase CT angiography)
    - For suspected
      - AMI (acute mesenteric ischemia)
      - IRCI (isolated right-colonic ischemia)
  - Angiography
    - CTA negative, but suspected
      - AMI (acute mesenteric ischemia)
      - IRCI (isolated right-colonic ischemia)
  - Colonoscopy
    - Within 48 h, using minimal air insufflation
    - Severe disease
      - Confirm localization of CI seen on CT
    - Biopsy
      - Except with severe disease / possible gangrene (peritoneal signs)

- Risk stratification (indicators of severe disease) – ICMR (ischemic colitis mortality risk)

	Odds ratio
• ≥ 3 of the following	
○ Clinical	
– Male - Abdominal pain but no rectal bleeding	3.90
– Hypotension	4.45
▪ SBP < 90 mm Hg	
– Tachycardia	4.40
▪ HR > 100 bpm	
○ Laboratory	
– ↑	
▪ WBC > 15 cells / mm (white blood cells)	
▪ LDH > 350-450 U/L (lactate dehydrogenase)	14.25
▪ BUN > 20 mg/dL (blood urea nitrogen)	4.35
– ↓	
▪ Hg < 12 g/dL (hemoglobin concentration)	4.5
▪ Albumin	
▪ pH (metabolic acidosis)	4.98
▪ Na+s < 136 mEq/L (serum sodium concentration)	
○ Colonoscopy	
– Ulceration of colonic mucosa	2.30
– Pancolitis	14.64
– R-colon only (IRCI)	5.75
• OR - - - -	
○ Clinical	
– Peritoneal signs	7.3
○ Diagnostic imaging pneumatosis	
– Venous gas in portomesenteric system	7.3
○ Colonoscopy	
– Gangrene	
– Distribution	
▪ Pancolitis	
▪ IRCI	5.75

Source: ACG Clinical Guideline, Brandt LJ, et al. Am J Gastroenterol 2015, page 31.

- Treatment
  - Mild disease
    - Supportive care
      - IV fluids
      - Correction of electrolytes
    - Observation
      - Type I CI no cause found
    - Correct any risk factor
      - Targeted therapy
  - Moderate / severe disease
    - As above for mild disease
    - Antibiotics (≥ 72 h)
      - Anaerobic plus
      - Fluoroquinolone, or aminoglycoside cephalosporin, 3rd generation
    - Surgical resection

- Prognosis

Outcome	Non IRCI	IRCI
30-day mortality	23%	12%
Surgery	55%	11%
Colectomy or death	59%	17%

  - Management
    - Medical (mild CI in 80%) ~ 6%
    - Surgical (severe CI in 20%) ~ 40%
  - Mortality rate with associated
    - COPD
    - CKD

Abbreviation: CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; IRCI, isolated right colonic ischemia;

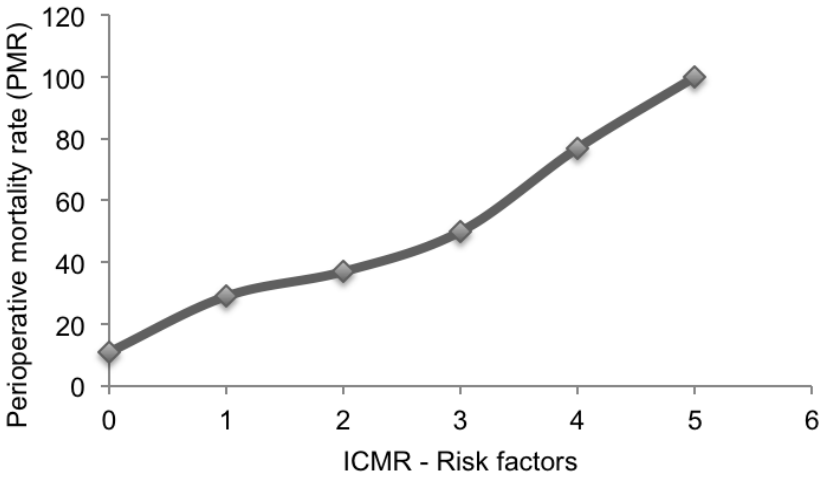
- Indications for surgery
  - Acute
    - Gangrenous bowel (peritoneal signs)
    - Bleeding, massive
    - Toxic megacolon (pancolitis)
    - Pneumatosis intestinalis
    - Venous gas, portomesenteric system
  - Subacute
    - Failure to respond with 2-3 wk to standard medical care recurrent sepsis
  - Chronic
    - Strictures
    - Symptoms from segmental CI

Adapted from: ACG Clinical Guideline, Brandt LJ, et al. Am J Gastroenterol 2015, Table 9, page 39.

  - Types of colectomy required
    - Total / subtotal ~ 40%
    - Right hemicolectomy ~ 35%
    - Segmental resection ~ 20%
    - Left hemicolectomy ~ 50%
  - Risk of perioperative mortality
    - Ischemic colitis mortality risk score (ICMR)
  - Perioperative mortality ~ 40% (depends on risk factors, e.g. ICMR [please see below])

- Comorbidities
  - Heart
    - Cardiac ejection fraction < 20%
  - Kidney
    - *AKI (acute kidney injury) requiring hemodialysis
  - Drugs
    - *Catecholamine (vasopressive) use pre- / intraoperatively

- Laboratory
  - *lactate > 2.5 mmol / L (preoperative value)
- Surgery
  - Total / subtotal colectomy
- Score 1 for each risk factor
- Predictive value of perioperative mortality with number of risk factors from ICMR



*predictive value of individual components of ICMR

Abbreviations: ICMR, ischemic colitis mortality risk score

- American Society of Anesthesiologists Status (ASA)

Predictors of perioperative mortality	Odds ratio
ASA class > 4	6.91
Post-operative hemodialysis for AKI	5.11
Bleeding > 500 mL	2.63
Intraoperative catecholamine (vasopressor) use	2.07
Lactate (peak preoperative value)	1.26

Abbreviation: AKI, acute kidney injury

- Give the names of 5 classes of medications which are associated with the development of colonic ischemia.
    - AAHC (antibiotic-associated hemorrhagic colitis
    - Chemotherapy
    - Cocaine
    - Constipation
        - Causing drugs, including 5-HT3 antagonists
        - Treating drugs
    - Decongestants (α1-adrenergics)
    - HRT (hormone replacement therapy), OCP (oral contraceptive pill)
    - NSAIDs

- Give 5 investigations for, and the **treatment** of acute mesenteric ischemia.

➢ Investigations
- Colonoscopy or flexible sigmoidoscopy, with mucosal biopsy
- Abdominal film
- Angiography
- CT angiography
- MRI
- 'Doppler ultrasound (shows only proximal vessels)
- Lab' – lactic acidosis, ion gap metabolic acidosis, hypercoagulopathy work up, anemia, leucocytosis
- Laproscopy, if high index of clinical suspicion of infarction

➢ Treatment
- Supportive
- Treat associated, underlying conditions
- Early surgery with resection for infarction/gangrene/perforation
- Embolectomy
- Papaverine
- Thrombolectomy
- Broad spectrum antibiotics if micro-perforation is suspected

Printed with permission: Sreenarasimhaiah J. *Best Pract Res Clin Gastroenterol* 2005;19 (2): pg 285-286.

STROMAL (MESENCHYMAL) TUMORS

- Types
  - GIST (gastrointestinal stromal tumors)
  - Often “dumbbell” shaped (intra- and extramural growth)
  - If not possible to distinguish between leimyoma and leimyona sarcoma, perform colectomy
  - Site
    - Stomach ~70%
    - Small bowel ~25%
    - Colon / rectum 5%
  - Malignant potential
    - All GISTs > 10 m

- Marker for GIST
  - C-kit (a stem cell factor receptor) (~99%)
    - CD34 (a hematopoietic cell progenitor cell antigen) (70%)
    - Smooth muscle actin (20% to 30%)
    - S 100 protein (marker of neural differentiation)
  - Miscellaneous
    - Fat
      - Lipoma
      - Liposarcoma
    - Muscle
      - Leiomyomas
      - Leimyosarcomas
    - Nerve
      - Schwannomas
    - Desmoid tumors
    - Endo- or exogastric (into or away from lumen, respectively)
    - Exogastric tumor displace rather than invade adjacent tissue
    - GIST and leiomyomas may be both endo- and exogastric, giving a dumbbell shape
    - GIT and leimyosarcomas
      - Usually exogastric
    - Leiomyomas are multiple in ~25%

- Diagnosis
  - EUS plus FNA
- Genetic mutations
  - Mutational activation of genes
    - KIT
    - PDGFRA
    - DC117
  - Medical treatment
    - TK (tyrosine kinase) inhibitors, e.g. imatimib, used as adjuvant or no adjuvant therapy (before surgical resection)
- Surgical treatment
  - Segmental resection for ≥ 2 cm; leaving the tumor pseudocapsule intact
  - Obtain negative tumor resection margins
  - Laparoscopic resection is possible
    Neoadjuvant therapy imatinib GISTs ≥ 3 cm
    ↓ GIST recurrence is post-op year 1
  - Neoadjuvant therapy with imatinib (a TKI) may be beneficial for distal rectal GIST

PERIANAL DISORDERS

Rectal Prolapse (aka Rectal Procidentia)

- Definition
  - Intussusception of the rectum, internally on itself, through the anus
    - Partial ▪ protrusion of the mucosa
    - Complete ▪ protrusion of all layers
- Demography
  - 15% to 30% of women with rectal prolapse have pelvic floor dysfunction or anatomic defects, e.g. rectocele, cystocele, enterocele

➢ Causes

- Give 10 factors which are associated with an ↑ risk of rectal prolapse (MG Varma and SR Steele, UpToDate May 2012)

➢ Differential

- Give the differential diagnosis of a complete rectal prolapse (has circumferential rings of mucosa).

  - Internal hemorrhoids, prolapsed
  - Rectal mucosa, prolapsed (partial prolapse)
  - Solitary rectal ulcer syndrome

➢ Investigation

- Give the menu of choices of investigations for suspected rectal prolapse.

  - Diagnostic imaging
    - Dynamic pelvic MRI
    - Cystocol po proctography
    - Fluoroscopic defecography
  - Pelvic physiological studies
    - Manometry
      - Results may be predictive of
        - Post-operative continence
        - Need for post-op' biofeedback
    - EMG (electromyography)
    - PNTML (pudendal nerve terminal latency)
  - White light colonoscopy +/- biopsy
  - Colonic transit study

- Treatment
  - Symptom management for constipation
  - Biofeedback for associated dyssynergic defecation (30% to 90% effective)
  - Surgical repair of pelvic floor

Anal Fissure

- Treatment
  - Objectives
    - Relax internal anal sphincter (IAS)
    - Ease passage of stool
    - Relieve pain

- Topical therapy
  - Nitroglycerin ointment 0.2 to 0.4% applied od-bid for 8 weeks
    - Mechanisms of action
      - ↑ local blood flow, especially to IAS
      - ↓ pressure, relaxing IAS

	Nitro	PL
- Healing	49%	36%
- Recurrence rate	~50%	

    - Do not use nitroglycerin (nitrates) within 24 hrs of taking sildenafil (Viagra®) for concern about hypotension

  - Diltiazem ointment (calcium channel blocker)
    - 2% ointment applied tid for 8 weeks
    - Healing 75% within 3 mon
    - Symptom free 66% during median follow-up of 32 weeks
    - Second course after 3 mon non-healing successful in ~80%
    - Switch from non-healing with nitroglycerin ointment to topical diltiazem ~50%
  - Bethanechol 0.1% ointment tid for 8 weeks
    - 60% healing

- Injection therapy
  - Botulinum toxin (BT)
    - ↓ release of acetylcholine from nerve endings
    - 5 to 10 units
      - Pain-free at 1 wk 63%
      - Healing at 3 mon 70%
      - Recurrence at 42 mon 42%

- Give the characteristics of persons treated with Botulinum toxin (BT) who relapse.

Characteristics	Relapse	No relapse
○ Anterior fissure (usually fissure (usually anal fissures are posterior)	45%	6%
○ Longer duration of anal fissure	59%	26%
○ Higher dose of BT to achieve initial healing	+	
○ Lower maximum anal squeeze pressure after BT injection	+	

Management

- Adding nitroglycerin ointment to BT injection accelerates healing at 6 weeks (66% vs. 20%), but not at 8 weeks or 12 weeks

- Oral therapies
  - Nifedipine 20 mg po bid, for 8 weeks
    - ↓ resting and maximum anal pressure
    - ↓ pain
    - Healing in 60%

- Comparisons

LIS Nif_T = BT > Nit_T > Diltiazem

Abbreviation: LIS, lateral internal sphincterotomy

Diltiazem po less effective at 8 wk then topical therapy (38% vs. 65%)

- Topical nifedipine (Nif_T) vs. topical nitroglycerin (Nit_T)

	Nif_T	Nit_T
Healing of anal fissure	89%	58%
AEs	5%	40%
Recurrence*	42%	31%

*42% after 183 weeks (Nif_T); 31% after 124 weeks (Nit_T)

- Nit vs. Botulinum toxin (BT) injection

	Nit_T	BT
Healing at 2 mon	60% to 70%	92% to 96%

Meta-analysis: Nit_T = bot; $Diltiazem_T$ = bot

- Surgery
  - Indicated for failure of medical therapy
  - Lateral internal sphincterotomy (LIS)
  - Comparisons
    - LIS vs. Nit_T

	LIS	Nit_T
Healing at		
5 wks	96%	67%
8 wks	97%	61%
10 wks	100%	89%

- LIS vs. BT

	LIS	Bot
Healing at		
2 mon	98%	64%
6 mon	96%	87%

  - Risk of
    - Minor fecal incontinence with LIS 30% to 45%
    - Recurrence with LIS ~8%

VOLVULUS

- Treatment
  - Neostigmine 2mg IV over 3-5 min with ECG monitoring to detect bradycardia. If no response in 4 minutes, repeat once (response rate>80%); if no response, perform decompression colonoscopy.
  - Contraindications to neostigmine: signs of colonic ischemia or perforation, bronchospasm, bradycardia, creatinine >3mg/dl, pregnancy.
  - Reduce the 35% risk of recurrence of megacolon by using 30g/day of PEG electrolyte solutions.
    - There is no proven benefit of placement of decompression tube.

"Help navigate outside the hospital setting

for the quality total care of your patient."

Grandad

LOWER GI BLEEDING

- Give the recommendation regarding the need to continue the use of aspirin or clopidogrel with endoscopic procedures with low or high risk of bleeding

Endoscopic procedure	Continue aspirin	Continue clopidogrel
• Low risk of bleeding		
○ EGD and colonoscopy ± biopsy	Yes	Yes
○ EUS without FNA	Yes	Yes
○ Digestive stenting	Yes	No
○ ERCP stent placement of papillary balloon dilation without endoscopic sphincterotomy	Yes	Yes
○ Argon plasma coagulation of angiodysplasia	Yes	Yes
○ Colonic polypectomy < 1 cm	Yes	**No**
○ Dilation of digestive stenosis	Yes	**No**
○ EUS with FNA of solid mass	Yes	**No**
• High risk of bleeding		
○ Esophageal variceal band ligation	Yes	**No**
○ EMR, ESD	**No**	**No**
○ Percutaneous endoscopic gastrostomy	Yes	NA
○ Endoscopic sphincterotomy	Yes	**No**
○ Ampullary resection	**No**	**No**
○ Endoscopic sphincterotomy + large balloon papillary dilation	**No**	**No**
○ EUS with FNA of cystic lesions	**No**	**No**
○ Colonic polypectomy > 1 cm	Yes	**No**

Note: Some authorities suggest that the risk of stopping aspirin (ASA) in a patient with an indication for ASA-prophylaxis is higher than the risk of bleeding, and that the ASA should always be continued

Abbreviations: EGD, esophagogastroduodenoscopy; EMP, endoscopic mucosal resection; ERCP, endoscopic retrograde cholangio-pancreatography; ESD, endoscopic submucosal dissection; EUS, endoscopic ultrasonography; FNA, fine-needle aspiration; NA not available;

Printed with permission: Blero D, et al. Endoscopic complications--avoidance and management. Nat Rev Gastroenterol Hepatol. 2012;9(3):162-72. Table 1.

HELPFUL WEBSITES

www.amazon.com

-To order less-than-cost paper book version of valuable Gastroenterology, Hepatology, Internal Medicine and other valuable textbooks.

www.cdc.gov/ncidod/srp/drugs/formulary.html

- CDA (Centers for Disease Control) and prevention drug service
e-mail parasites@cdc.gov
phone: 1-404-639-3670

www.hpa.org.uk

- British resource that looks to protect and improve the nation's health and wellbeing, and reduce health inequalities.

www.giandhepatology.com

-Website with fantastic resources for physicians.

www.motherisk.org/women/index.jsp

-Check Up-To-Date safety of all drugs before prescribing in pregnancy and lactation.

www.worldgastroenterology.org

-Excellent guidelines developed by WGO, World Gastroenterology Organization

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